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RADIOACTIVE SODIUM (Na^{24}) IN THE MEASUREMENT OF LOCAL BLOOD FLOW

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THIS study was made to determine whether the clearance rate of radioactive sodium (Na^{24}) from muscle after intramuscular injection would measure muscle blood flow indirectly. Radioactive isotopes have been used in various ways in the study of peripheral vascular disease. The material may be introduced intravenously and the concentration at the periphery determined. Smith and Quimby[1] thought that the rate of increase and the final level thus obtained were often related to the degree of pathological change, but commented that patients with peripheral vascular disease may fall "below, within or above" the range of normals. Friedell and associates[2,3,4] have used radioactive phosphorus (P^{32}) similarly. Kety[5] measured the local clearance of radioactive sodium after intramuscular injection. As this tracer substance is readily diffusible, he believed that the clearance rate would depend on the local tissue circulation and further that it might measure it. He stated that serial counts received from the tissue deposit of Na^{24} should decrease along a single exponential curve which, plotted semilogarithmically with respect to time, should yield a straight line and that the slope of this line would be a quantitative measure of the total ability of the local circulation to remove and to supply freely diffusible substances. Na^{24} was chosen for the present study because it is easily diffusible and has a short half life (14.8 hours), which makes its use safe in small quantities, and because Kety's hypothesis appeared sound. Both methods, i.e., that of Smith and Quimby,[1] involving the concentration of radioactive sodium in the tissues of the extremities after intravenous injection, and that of Kety,[5] based on the rate of disappearance of radioactive sodium when injected intramuscularly, have been discussed and used by Elkin and co-workers[6] and Cooper and associates.[7]

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The method in the present study was a modification of that described by Kety.[5] Measurements were made in normal individuals of different ages and in patients with intermittent claudication. An attempt was made to select patients whose claudication pain appeared to come from the gastrocnemius muscle into which the injection was made. The criteria employed were those of Boyd and co-workers[8] who used the method of Lewis and Kellgren[9] to determine the segmental reference of deep pain from the gastrocnemius muscle.

MATERIAL

Three groups of subjects were studied.

1. Eleven healthy men and women between the ages of 21 and 32 years. On these eighteen observations were made.
2. Ten men and women between the ages of 45 and 70 years with no clinical evidence of vascular disease. On these ten observations were made.
3. Thirteen men and women over the age of 45 years with occlusive arterial disease of the legs and the symptoms of intermittent claudication. Pain in the calf on exercise was a feature of all these cases. On these fourteen observations were made.

In all, forty-two observations were carried out on thirty-four subjects of all groups.

METHOD

The usual precautions in the clinical use of radioactive compounds were observed. The maximum dose of radiation to the local tissues with the method used is not excessive (approximately 5 roentgens). Careful note was taken of the subject's activity before the intramuscular injection of Na^{24}. Subjects rested for at least forty minutes before the experiment, as preliminary observations suggested that thirty minutes of rest were essential to obtain basal readings.

Isotonic sodium chloride solution (0.5 ml.) containing 5 microcuries of Na^{24} was injected into the calf in the midline posteriorly, 12 cm. below the bend of the knee and to a depth of 2 cm. During this operation and subsequently, the subject lay prone on an examination couch. The feet were allowed to hang comfortably over the end, and the chest was supported with pillows. A Geiger-Müller counter was fixed in position above the site of injection, resting on the skin but without exerting any pressure on the soft tissues of the leg.

Serial counts were made at minute intervals for at least ten minutes, and clearance rates at rest were calculated. It was not practical to take readings during walking, but readings were made immediately after it in a number of subjects. After the initial rest and subsequent readings at rest, subjects exercised on a moving walking platform. Postexercise readings were begun within 40 seconds of the end of the exercise. An ideal, difficult to achieve under clinical conditions, would have been some exercise in which the work done by the gastrocnemius muscle itself was standardized. As an alternative, walking was chosen as being a form of exercise which normally produced leg pain in patients with

TABLE I. RESULTS IN THE THREE GROUPS

GROUP 1 GROUP 2 GROUP 3

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GROUP 1 (NORMAL ADULTS 20 TO 32 YEARS)						GROUP 2 (ADULTS WITHOUT VASCULAR DISEASE; 45 YEARS AND OVER)						GROUP 3 (INTERMITTENT CLAUDICATION CASES)					
SUBJECT	SEX	AGE	RESTING HALF DISPERSAL TIME (T) (MINUTES)	EXERCISE (FEET IN MINUTES)	POSTEXERCISE HALF DISPERSAL TIME (T^x) (MINUTES)	SUBJECT	SEX	AGE	RESTING HALF DISPERSAL TIME (T) (MINUTES)	EXERCISE (FEET IN MINUTES)	POSTEXERCISE HALF DISPERSAL TIME (T^x) (MINUTES)	SUBJECT	SEX	AGE	RESTING HALF DISPERSAL TIME (T) (MINUTES)	EXERCISE* (FEET IN MINUTES)	POSTEXERCISE HALF DISPERSAL TIME (T^x) (MINUTES)
1	M	32	43			1	M	52	21	420 in 2	27	1	M	60	13	416 in 2 (P)	6.7
2	M	21	40			2	M	59	22	420 in 2	10	2	F	74	9.5	416 in 2	14
3	M	22	26			3	M	60	29	420 in 2	22	3	M	57	24.5	416 in 2	+++
4	F	23	18 22.5	212 in 2	14	4	M	68	17.5	420 in 2	8	4	M	45	29	416 in 2 (P)	6
5	M	23	40 24	212 in 2	22	5	F	55	26.5	420 in 2	12	5	M	61	13	416 in 2 (P)	9
6	F	22	24 30	212 in 2	15	6	F	50	45	420 in 2	18	6	M	69	18		
7	M	22	32 37	212 in 2 628 in 2	39 34	7	M	74	33	420 in 2	16.5	7	F	64	26		
8	F	26	16.5 21	210 in 2 630 in 2	25.5 20	8	M	63	28			8	M	52	22.5 9.5	100 x dorsiplantar flexions	11
9	M	24	16 15.5	640 in 2	20	9	M	53	14			9	M	61	20	623 in 3 (P)	9
10	F	25	21	661 in 2 5,280 in 17	10 8	10	M	47	19			10	M	62	14	623 in 3	7
11	M	28	12									11	M	56	13.5	623 in 3 (P)	11
												12	M	72	10.5	623 in 3 (P)	11
												13	M	57	25	1,330 in 6 (P)	23
Means			25.8 σ = 9.3						25.5 σ = 8.5						17.7 σ = 6.7		

Both legs were examined where two figures are shown opposite one individual. These examinations were carried out at different times.
*(P) = pain in calf.

intermittent claudication. Exercise was controlled as far as possible under the circumstances, but some patients with intermittent claudication were unable to complete a standard amount of exercise because of the occurrence of pain and fatigue. Three grades of exercise were used in the experiments.

1. Mild: 212 feet in 2 minutes (1.76 feet per second)
2. Moderate: 416 to 420 feet in 2 minutes (3.46 to 3.50 feet per second)
3. Severe: 620 to 660 feet in 2 minutes (5.1 to 5.5 feet per second)

None of the intermittent claudication group was able to do the severe grade of exercise; some performed the second grade of exercise for three minutes instead of two minutes and one for six minutes. One normal subject walked 5,280 feet in seventeen minutes.

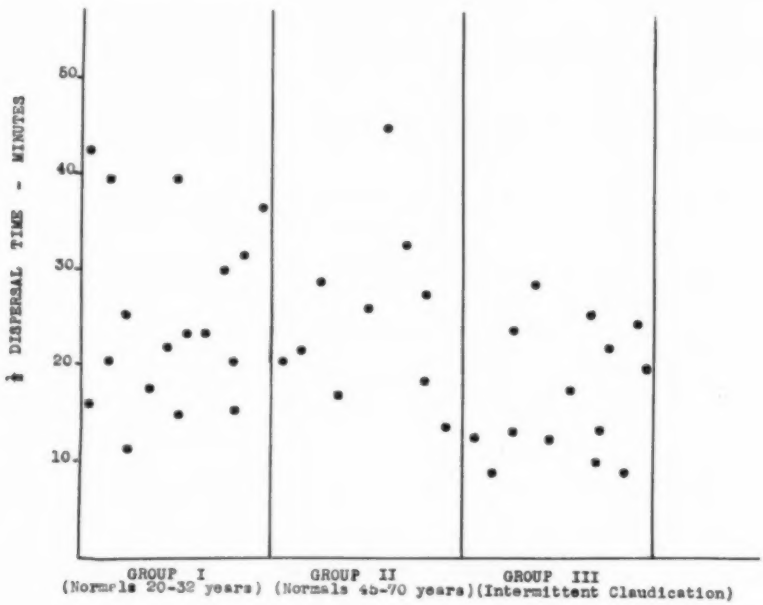

Fig. 1.—Clearance rates (half dispersal times) in the three groups.

Examinations were always performed in the same room where the temperature varied between 18.5 and 21.5° C.; humidity was not determined. These variations in room temperature did not appear to have any significant effects on clearance rates.

CALCULATION

Kety[5] predicted on theoretical grounds that the dispersal of the Na^{24} from the site of injection would show an exponential decrease with time and verified this experimentally. The time taken by the radioactive material to decrease by one-half after injection represents its rate of dispersal. This is termed the "half dispersal time."

The counting rate, as indicated on the scale of a counting rate meter receiving pulses from the Geiger counter, shows the quantity of radioactive material

present at the site of injection. It was plotted directly on to semilogarithmic paper with time in minutes plotted as the abscissa. From the straight line thus obtained, the half dispersal time was measured directly.

RESULTS

The results are expressed as the half dispersal times described above. For the purpose of this paper, T equals half dispersal time at rest, and T^X equals half dispersal time after exercise. Results are shown in Table I. Clearance rates at rest in all three groups are shown diagrammatically in Fig. 1. If the resting values of T as found in Groups I and II are compared, it will be seen that the means and standard deviations are practically identical. If Group II is compared with Group III, it is seen that the mean T value in Group II is 25.5

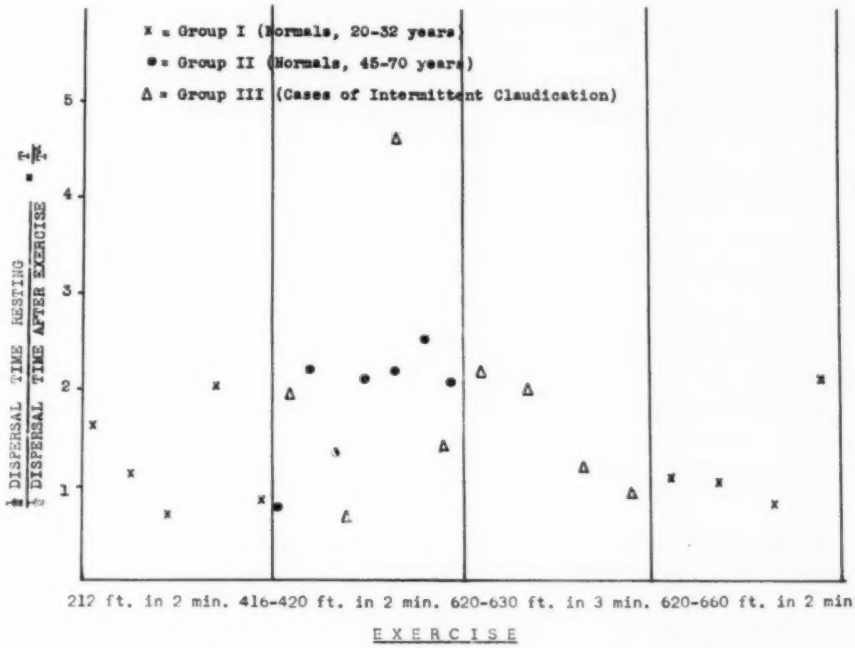

Fig. 2.—Ratio of resting to postexercise half dispersal time (T/T^X ratio) in all groups after different grades of exercise.

seconds with σ equalling 8.5, whereas in Group III (intermittent claudication patients) it is 17.7 seconds with σ equalling 6.7. The difference between the means of the two groups has no statistical significance. Together with the amount of exercise taken, the values of T^X (half dispersal time after exercise) are shown in Table I. Although in most instances T^X is shorter than T, the effects of exercise are unpredictable, and there is no constant change after exercise in any group. The value of T varied so widely from one subject to another that an attempt was made to relate T to T^X by means of a ratio, $\frac{T}{T^X}$. This ratio is

plotted in Fig. 2 against the severity of the exercise. There is neither a fixed relation to the severity of the exercise nor any difference between the three groups tested.

COMMENT

The values for T (resting) for normals, as recorded both in this paper under conditions standardized to the extent described and by Cooper and associates,[7] varied widely. Cases of intermittent claudication, included in this study, fell within the normal range. Similarly, in our experiments the ratio of half dispersal time before exercise to half dispersal time after exercise ($\frac{T}{T^x}$ ratio) showed a wide variation. Both normals and patients with claudication carrying out widely varying grades of exercise fell within the same range. From these results there are two possible conclusions. Either the Na^{24} clearance did not measure muscle blood flow, or muscle blood flow in the patients with intermittent claudication and obliterative arterial disease did not differ from normal under the conditions of the experiment. It appears to us that the former is the more probable. The findings of Shepherd[10] are against the latter alternative. He showed that immediately after exercise patients with intermittent claudication had either a diminished blood flow in the calf compared with the resting level or an increase which was much less than that found in normals.

In the light of these findings the suggestion of other workers that this method may be used to assess the effects of therapy in peripheral vascular disorders[7] seems at present to be unjustified. It is thought that the relation between muscle blood flow and the Na^{24} clearance rate can only be established when the two have been correlated with simultaneous direct measurement of blood flow and estimation of Na^{24} clearance. It appears from available evidence that there is no fixed relation between the two.

SUMMARY

1. Forty-two observations in thirty-four subjects of the rate of clearance of Na^{24} from the gastrocnemius muscle were made. The subjects included normals of different ages and patients with intermittent claudication.

2. Clearance rates in these groups before and after exercise were determined.

3. The significance of the results is discussed.

We wish to thank Professor A. Kekwick and Professor J. E. Roberts for their encouragement in this project, the medical students and others who acted as normal controls, and the nursing and clerical staffs of the Professorial Medical Unit for their willing help.

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CONSISTENCY OF CLEARANCE OF RADIOACTIVE SODIUM FROM HUMAN MUSCLE

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A METHOD for the measurement of effective blood flow using the clearance of radiosodium (Na^{24}) from tissue has recently been described.[1] This method was used in acute experiments. It appeared to us that the value of the technique would be increased if it could be shown that the rate of clearance is reproducible within relatively narrow limits over an extended period of time.

In the present study, we repeatedly determined the clearance rate of radiosodium from the gastrocnemius and biceps muscles of normal subjects at rest, during moderate exercise, following fatiguing exercise, and during postural changes over a period up to three months.

METHOD

The subjects for the experiment were normal white men, most of whom were between 25 and 40 years of age. In all experiments, the subject was permitted to rest on a table for twenty minutes before beginning the experiment. An attempt was made to perform the experiments on each individual at approximately the same time of day and to maintain the temperature of the laboratory between 75° and 80° F.

In every experiment, between 0.05 and 0.1 c.c. of isotonic sodium chloride solution containing between 1 and 4 microcuries of Na^{24} was injected.

In the gastrocnemius muscle, all injections were made by inserting the needle to the hilt into the belly of the muscle using a 20 gauge 1½ inch needle. This was done to insure approximately the same depth of injection in the same subject in all determinations. In each of ten subjects, five separate injections were made, the time between injections ranging from one day to several months.

Immediately after injection of the radiosodium, a thin, mica window Geiger counter was placed in a fixed position over the injection site. The activity at the site was recorded using a scaling circuit with scale selection of 16, 32, 64. The register readings were recorded at one-minute intervals for twenty minutes. The counting was then discontinued. After an interval of one to three hours, the counting rate over the injection site was again determined.

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In the biceps muscle the same procedure was followed except for the use of 22 gauge 1 inch needles for the injections. Each of six individuals received five injections.

In experiments on moderate exercise, the biceps muscle was used. A lightweight Geiger counter was supported in a counterbalanced mount and lightly taped to the arm. The counting rate over the injection site was continuously determined, first for four to five minutes while the arm was at rest and then for four to five minutes more as the subject lifted a 5 pound weight by flexing the arm from 180 degrees to 90 degrees.

In those experiments involving fatigue, the patient exercised the biceps muscle by resting the elbow on a table and lifting a 15 pound weight from 180 degrees to 75 degrees twenty times a minute until he complained of considerable fatigue. The injection was then made in the fatigued biceps muscle and the subsequent counting procedure was as previously described. Control readings with the patient at rest had previously been determined.

The effects of postural changes on the clearance of radiosodium from the gastrocnemius muscle were determined. First, control readings were made with the subject horizontal and at rest for several minutes. The subject was then either tilted on a tilt table to 80 degrees or asked to stand, and the readings were continued for several more minutes.

The data are plotted on semilogarithmic paper as a function of time. The clearance half life is the time it takes for the activity initially present to be reduced to one-half. The clearance constant (K) is equal to the natural logarithm of two divided by the clearance half life ($K = \frac{0.693}{T\,\frac{1}{2}}$).

In each subject, three curves were plotted from the data, and the separate clearance half lives and clearance constants were determined. The average half life and average clearance constants were determined, and then standard deviations were calculated. The range is given as the average value ± (plus and minus) twice the standard deviations.

Following this, two further clearance constants were found on each individual and were compared with the predicted range.

RESULTS

The rate of clearance in a normal subject remains constant within a relatively narrow range over long time periods. The clearance constant averages for the various individuals in this study were variable from individual to individual. In the gastrocnemius muscle this range was from 0.0533 to 0.0684 minute^{-1}; in the biceps muscle the range of clearance constant averages was from 0.0579 to 0.1271 minute^{-1}. In general, the ranges established for each individual from the formula, range = average ± 2 times standard deviation, did not exceed ± 20 per cent of the average clearance rate for the particular individual and was less in most cases.

TABLE I. GASTROCNEMIUS MUSCLE

AVERAGE CLEARANCE (MINUTES $^{-1}$)	PREDICTED RANGE (MINUTES $^{-1}$)	SUBSEQUENT DETERMINATIONS (MINUTES $^{-1}$)	PREDICTED RANGE IN HALF LIFE (MINUTES)	SUBSEQUENT DETERMINATIONS IN HALF LIFE (MINUTES)
1. 0.0684	0.0558–0.0810	1) 0.0633 2) 0.0633	8.6–12.4	1) 11.0 2) 11.0
2. 0.0654	0.0562–0.0746	1) 0.0730 2) 0.0746	9.2–12.2	1) 9.5 2) 9.25
3. 0.0614	0.0506–0.0722	1) 0.0506 2) 0.0605	10.4–13.7	1) 13.5 2) 11.25
4. 0.0557	0.0453–0.0661	1) 0.0472 2) 0.0506	10.5–15.2	1) 14.5 2) 10.5
5. 0.0630	0.0558–0.0702	1) 0.0580 2) 0.0693	9.9–12.4	1) 12.0 2) 10.0
6. 0.0584	0.0540–0.0628	1) 0.0647 2) 0.0647	11.0–12.8	1) 10.75 2) 10.75
7. 0.0533	0.0462–0.0604	1) 0.0514 2) 0.0491	11.5–15.0	1) 12.25 2) 14.0
8. 0.0565	0.0511–0.0619	1) 0.0714 2) 0.0613	11.0–13.5	1) 9.75 2) 11.0
9. 0.0633	0.0532–0.0734	1) 0.0605 2) 0.0647	9.5–13.1	1) 11.5 2) 10.75
10. 0.0625	0.0517–0.0733	1) 0.0647 2) 0.0580	9.5–13.4	1) 10.25 2) 12.0

TABLE II. BICEPS MUSCLE

AVERAGE CLEARANCE (MINUTES $^{-1}$)	PREDICTED RANGE (MINUTES $^{-1}$)	SUBSECUENT DETERMINATIONS (MINUTES $^{-1}$)	PREDICTED RANGE IN HALF LIFE (MINUTES)	SUBSEQUENT DETERMINATIONS IN HALF LIFE (MINUTES)
1. 0.0597	0.0490–0.0704	1) 0.0506 2) 0.0647	9.8–14.0	1) 13.75 2) 10.75
2. 0.0924	0.0842–0.1006	1) 0.0990 2) 0.0840	6.9– 8.3	1) 7.0 2) 8.25
3. 0.0777	0.0652–0.0902	1) 0.0693 2) 0.0771	7.7–10.6	1) 10.0 2) 9.0
4. 0.0905	0.0776–0.1034	1) 0.0991 2) 0.0815	6.7– 8.8	1) 7.0 2) 8.5
5. 0.0671	0.0566–0.0776	1) 0.0676 2) 0.0576	8.8–12.2	1) 11.0 2) 11.0
6. 0.1271	0.1021–0.1521	1) 0.1026 2) 0.1026	4.5– 6.8	1) 6.75 2) 6.75

Following the establishment of a range for each individual, two more determinations of clearance rates were made and compared with the range. These determinations were made from one week to two months after the range had been established. These results are given in Tables I and II. Fig. 1 is a typical set of curves showing the predicted range and two subsequent determinations for a single individual. In only one determination, or 3.2 per cent of the studies, was

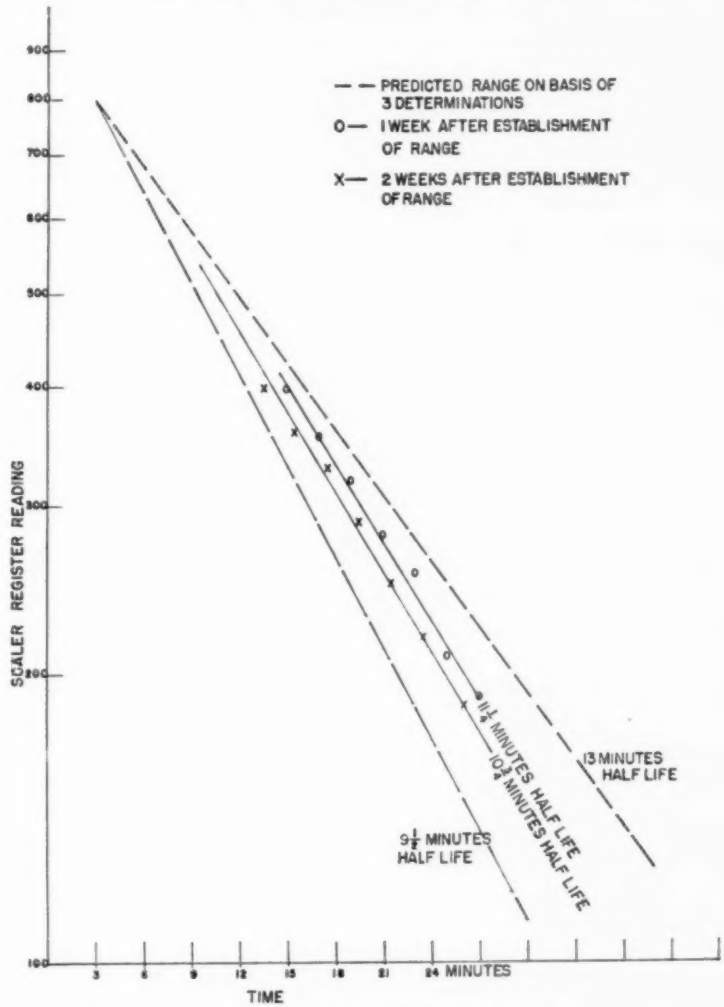

Fig. 1.—Predicted range and two subsequent clearance curves.

the clearance constant significantly outside the predicted range. Two determinations were just outside the predicted range. Since the formula on which the ranges were based predicts that only 95 per cent of all future determinations will be within the calculated range, the error of 3.2 per cent was expected.

As can be seen from the tables, the clearance constants for the biceps muscles indicate a slightly greater rate of effective blood flow than in the gastrocnemius muscles at rest.

On moderate exercise the clearance from the biceps muscle increased more than 100 per cent within thirty seconds (the interval between counts in this series of experiments) as shown in Fig. 2. If, as in one of our subjects, the average resting clearance constant of the biceps muscle was 0.0671 minute^{-1}, the clearance rate average during manual exercise was 0.2540 minute^{-1}. This is an increase in effective blood flow of just under 400 per cent. In reproducing these experiments over a two-week period in the same subject, the clearance constants ranged between 0.232 and 0.3470, or a range of ± 25 per cent average. Since the amount of work was only approximately equal from experiment to experiment, the wider range during exercise than at rest can easily be understood.

Fatiguing exercise of the biceps muscle resulted in a more rapid clearance rate as compared with the resting rate of the biceps. Fig. 3 is a typical graph showing the effect of this exercise. This rapid rate persisted for six to eleven minutes, depending on the training of the individual. Following this initial rapid

Fig. 2.—Effect of moderate exercise on the clearance from biceps muscle.

rate, there was a gradual return to the rest clearance with a trend toward its upper limit. For example, in one of our experiments, the resting clearance average was 0.0905 minute^{-1}. Immediately after fatiguing exercise, the clearance rate average was 0.1734 minute^{-1} for seven to ten minutes, and after this interval the rate was 0.1025 minute^{-1}, which was the upper limit of the resting range for this subject. In all experiments involving fatiguing exercise, the clearance constants were reproducible within a ± 20 per cent of the average.

Postural changes in the subjects being tested had no significant effect on the clearance of radioactive sodium from the gastrocnemius muscle. Fig. 4 is a typical graph showing the effect of postural changes. When a subject was tilted to an angle of 80 degrees on a tilt table, the curve found was well within the previously established horizontal testing range.

In standing, counting should not begin for two to three minutes so that the effect of muscular activity involved in moving from the horizontal to the standing position will not mask the clearance rate for the standing subject. In this study the curves found for the subject in the vertical position were within the range for the individual at rest and prone.

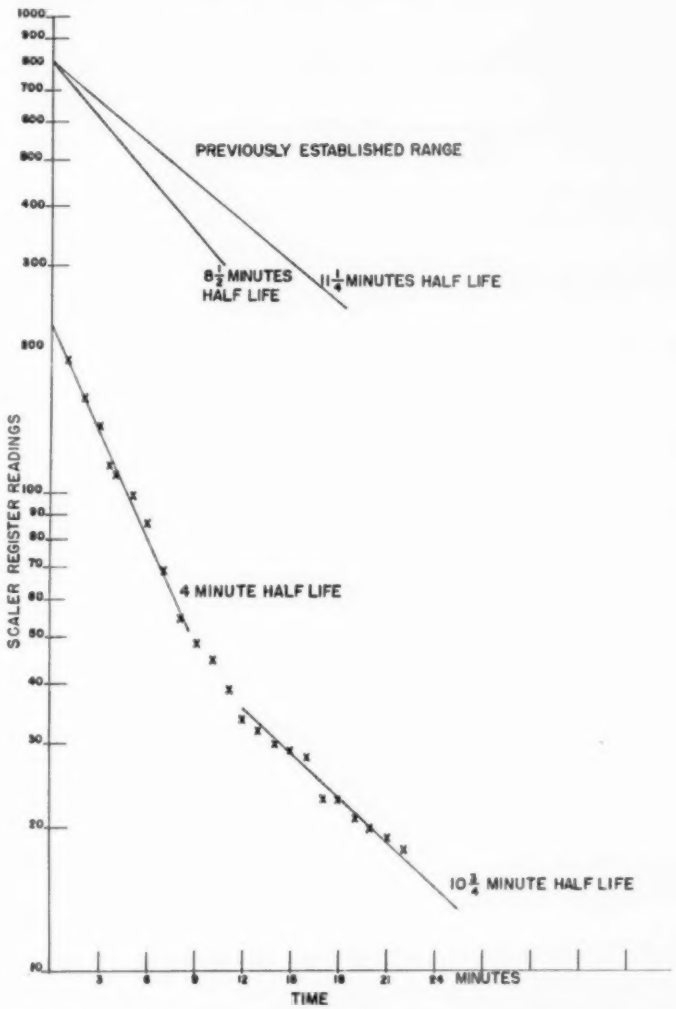

Fig. 3.—Effect of fatiguing exercise on the clearance from the biceps muscle. Counting began only after the subject had developed fatigue in exercising the muscle.

DISCUSSION

It has been shown previously that the decrease in activity of radiosodium in a tissue per unit of time is proportional to the activity originally injected.[1] Therefore, the radioactivity deposited within a tissue decreases exponentially with time. If the activity is plotted as a function of time on a semilogarithmic graph, the plotted points should be along a straight line.

The total counting rate measured over the injection site is made up of the following factors: (1) the natural background of the counter, (2) the counting rate resulting from the dispersal of Na^{24} throughout the body via the blood stream, (3) the counting rate resulting from Na^{24} spilled on the skin, (4) the counting rate resulting from Na^{24} in the subcutaneous tissue deposited when the needle is withdrawn after injection is made, and (5) the counting rate of the Na^{24} in the muscle.

When our technique is used, (1) and (2) are less than 1 per cent of the total counting rate, and (3) can be avoided if care is taken when the injection is made.

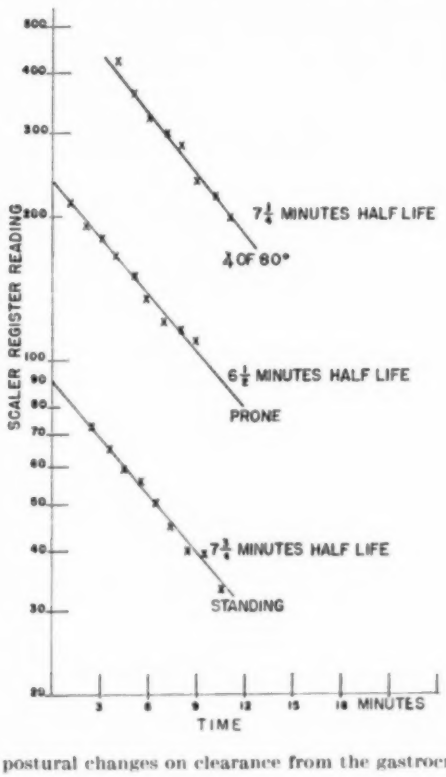

Fig. 4.—Effect of postural changes on clearance from the gastrocnemius muscle.

This background (1), (2), (3) is adequately accounted for by subtracting from the total counting rate, the counting rate over the site injected, one to three hours after the injection. Since this background is small compared with the total counting rate, it is not necessary to correct for the decay of the radiosodium.

Number (4), the counting rate of the Na^{24} in the subcutaneous tissue, is of significance because the clearance from this tissue has been reported as markedly slower than that from muscle.[2,3] The amount present in the subcutaneous tissue is small compared with the amount present initially in the muscle. However, after about twenty minutes the Na^{24} in the muscle has been cleared to a large extent, and the amount still present in the subcutaneous tissue becomes a significant fraction of the total being counted. The time before which the Na^{24} present

in subcutaneous tissue will reach a significant value will depend on the relative amount initially injected into the muscle and subcutaneous tissue. A semilogarithmic plot of the raw data will be a curve if taken over a long period of time (about one hour) because it represents the clearance from two depots, muscle and subcutaneous tissue.

The background taken one to three hours after the injection does not adequately account for the activity within the subcutaneous tissue since in this time it has cleared appreciably. However, the smaller the amount in the subcutaneous tissue, the smaller the error.

The net counting rate due to the activity of Na^{24} in the muscle is obtained by subtracting from the total counting rate, the rate over the site of injection one to three hours later. This net counting rate should be large compared with the other rates previously described for the first twenty minutes following the injection. Hence, if the subject is kept at rest for this interval, the semilogarithmic plot of the net counting rate as a function of time is a straight line.

It has been demonstrated that fairly long time intervals (one week to three months) between experiments have no significant effect on the rate of clearance of Na^{24} from the biceps and gastrocnemius muscles of normal subjects. Reproduction of clearance curves in the same individual is therefore possible within a predictable range, if there has been no pathological change, for long time periods. The method then may be used as a measure of gross changes of blood flow over a considerable period of time. Since peripheral vascular diseases are chronic, such a method is of definite advantage in studying the natural course of disease or the effect of therapeutic measures.

This method is the only one available in which the effective blood flow in muscle can be directly measured, rather than ascertaining indirectly the total flow in a limb.

The authors feel that if an arbitrary error of $\pm$ 20 per cent is attached to the average of three separate determinations of the clearance of Na^{24} from muscle, the great majority of future determinations (well over 95 per cent) will fall within the range so established.

No estimate can be made at the present time as to how much of the $\pm$ 20 per cent variation in clearance rate is a result of normal physiological variations and how much is a result of inherent error in the method.

SUMMARY

1. Clearance of radioactive sodium from the gastrocnemius and biceps muscles in normal men is reproducible over periods of time up to three months.

2. Moderate exercise will significantly increase the rate of clearance of radioactive sodium from muscle within thirty seconds from the start.

3. Fatiguing exercise will markedly increase the rate of clearance of radioactive sodium from muscle, and this increase will be maintained for several (eight to ten) minutes following the cessation of fatiguing exercise.

4. Postural changes have no effect on the clearance rate of radioactive sodium from the gastrocnemius muscle.

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ATYPICAL PATENT DUCTUS ARTERIOSUS WITH ABSENCE OF THE USUAL AORTIC-PULMONARY PRESSURE GRADIENT AND OF THE CHARACTERISTIC MURMUR

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THE clinical criteria for the diagnosis of patent ductus arteriosus are well known and are, in the vast majority of cases, sufficient to establish the diagnosis without recourse to cardiac catheterization or to angiocardiography. Of these criteria, a continuous machinery murmur best heard at the left of the upper sternum has been considered typical of patent ductus and is rarely of other origin (i.e., arteriovenous aneurysm in the same area). However, the earlier insistence that this typical murmur must be present in order to justify surgical exploration[1,2] has proved untenable. Furthermore, it has been pointed out[3,4] that in infancy or with congestive heart failure a patent ductus may be present without murmurs. Several proved cases[3,5] have been reported in which only systolic murmurs not continuing into diastole were found. Why does a patent ductus arteriosus occasionally fail to give rise to a continuous murmur? Burchell[5] suggested that in these cases the usual aortic-pulmonary pressure gradient may be absent during diastole or during the entire cardiac cycle. However, no data bearing on this point have thus far been available.

In this paper we present two cases of patent ductus arteriosus in children who did not exhibit the classic machinery murmur. In the preoperative evaluation of these patients, cardiac catheterization was helpful in making the diagnosis and, in one of the cases, furnished data which satisfactorily explained the lack of typical physical signs.

CASE REPORTS

CASE 1.—This 6-year-old white boy was admitted to the hospital on Nov. 30, 1948. His mother stated that she had had "measles" during the first trimester of pregnancy. Delivery was uneventful, although one month premature. No cyanosis or other abnormality was noted at birth. Development was normal except that he was small for his age and appeared to tire easily. He suffered from frequent upper respiratory infections. When the child was 3 months old, a cardiac abnormality was noted by the family physician. At the age of 5 years he had measles and mumps simultaneously and for the first time developed transient cyanosis, for which he was given oxygen therapy and digitalis.

Physical examination on admission revealed a small, pale child, in the lower ten percentile for both height and weight. There was no cyanosis or clubbing. The blood pressure was 90/60

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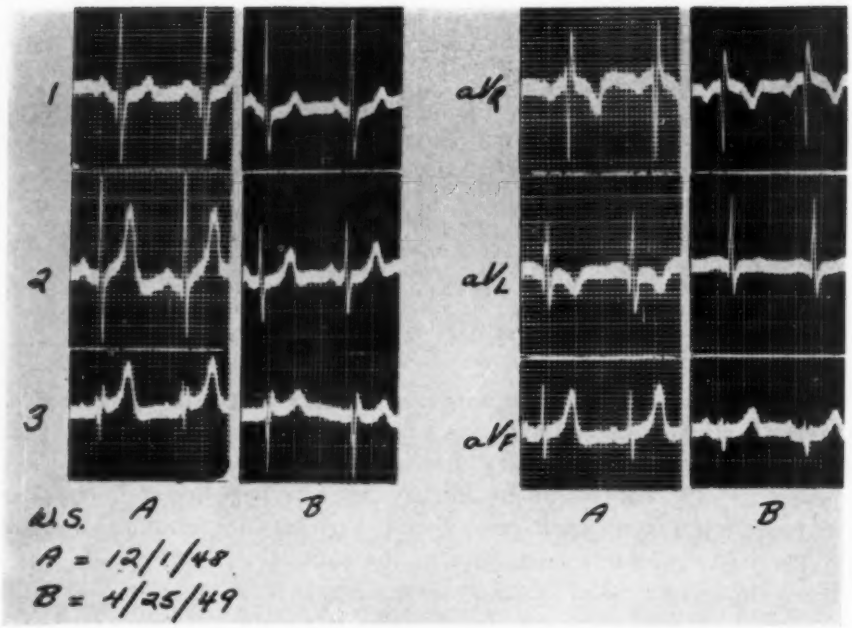


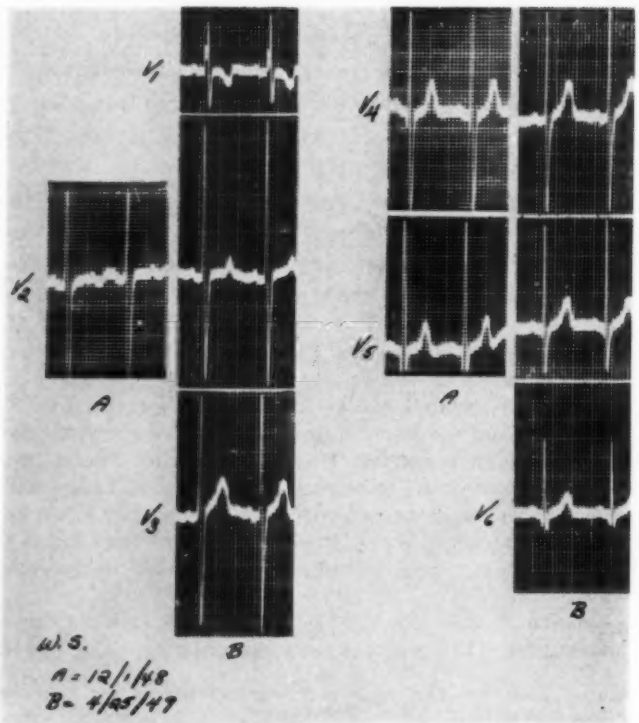
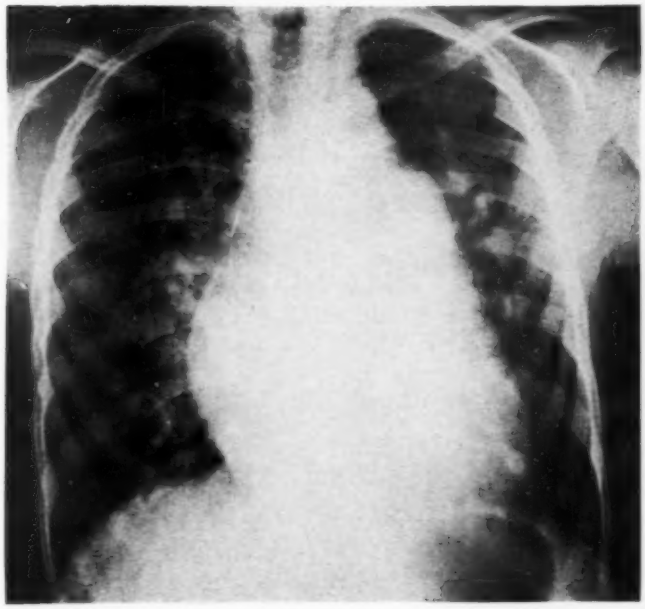
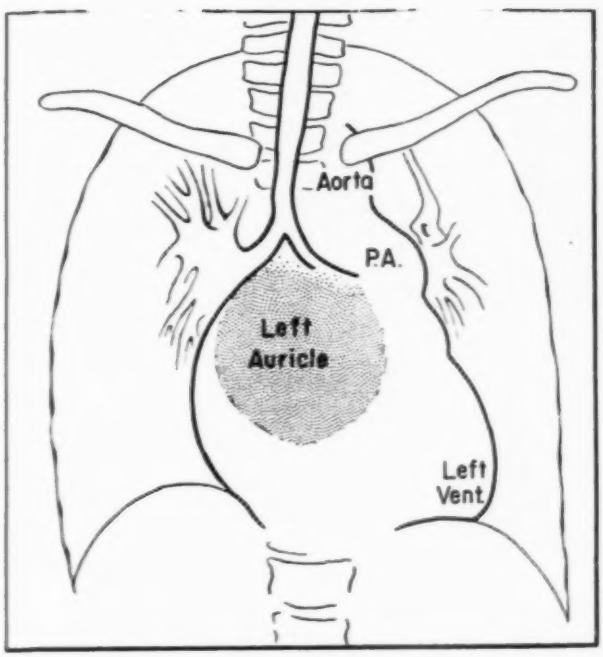


Fig. 1 (Case 1).—*A*, Preoperative electrocardiograms suggesting both right and left ventricular hypertrophy. *B*, Electrocardiograms taken four months postoperatively.



A.



B.

Fig. 2. *A* and *B* (Case 1).—*A*. Preoperative x-ray film showing cardiac enlargement and engorgement of the hilar vessels. *B*. Line drawing of *A*, demonstrating the position of the enlarged left auricle which gives a double contour to the right heart border.

mm. Hg; the pulse was 92 per minute and regular. A prominent arterial pulse was present in the neck, particularly in the suprasternal notch. The heart was moderately enlarged to the right and to the left. There was a loud, rather long third heart sound (questionably a mid-diastolic murmur) at the apex. There was a Grade 4 systolic murmur, associated with a thrill, most marked in the suprasternal notch and in the second and third intercostal spaces both to the right and left of the upper sternum but widely transmitted over the precordium, neck, shoulders, and posterior chest. The pulmonary second sound was greatly accentuated and was followed by an early, high-pitched, Grade 2 decrescendo murmur well heard at the pulmonic area and along the left sternal border. At no time was there observed a clear-cut machinery murmur typical of a patent ductus. However, on repeated auscultation the same observers at times suspected and at times dismissed the possibility of an indistinct continuous murmur in addition to the early diastolic murmur in the pulmonic area. A tender liver edge was palpable 2 cm. below the right costal border. Arterial pulsations in the lower extremities were normal.

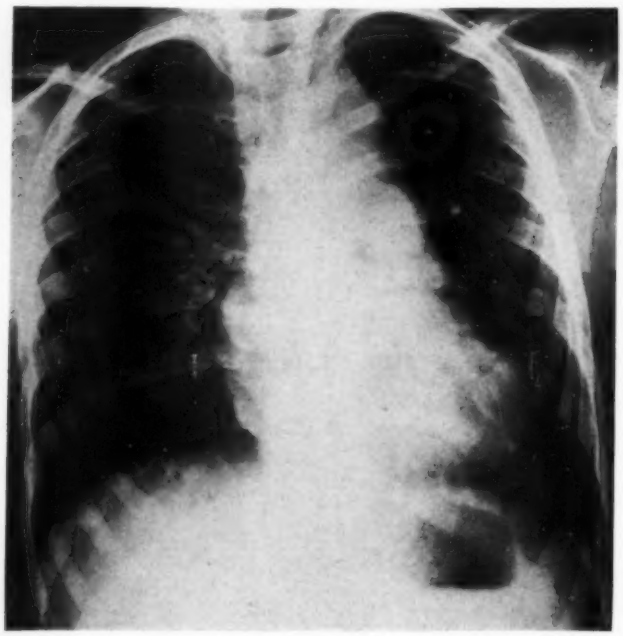


Fig. 2, *C*.—Roentgenogram taken four months after operation showing decrease in heart size and hilar vessel congestion.

An electrocardiogram (Fig. 1,*A*) with particular reference to Lead aV_L and to the unipolar chest leads suggested the presence of both right and left ventricular hypertrophy. An x-ray film of the chest (Fig. 2,*A* and *B*) indicated generalized enlargement of the heart with great increase in size of the main pulmonary artery and the hilar and pulmonary vascular markings. Fluoroscopically, pulsations of the pulmonary artery and its branches were definitely accentuated without rapid diastolic collapse.

A phonocardiogram (Fig. 3,*A*) indicated a loud third heart sound at the apex, followed by a diastolic murmur, and confirmed the presence of a systolic murmur at the base and a prominent second sound at the pulmonary area, followed by an early high-pitched diastolic murmur. As seen in Fig. 3,*D*, some of the complexes resembled those of pulmonary regurgitation while others suggested a continuous murmur.

A cardiac catheterization was performed (see Table I). The data indicated right ventricular and pulmonary hypertension with a significant increase in the oxygen content of blood samples taken from high in the right ventricle and from the pulmonary artery.

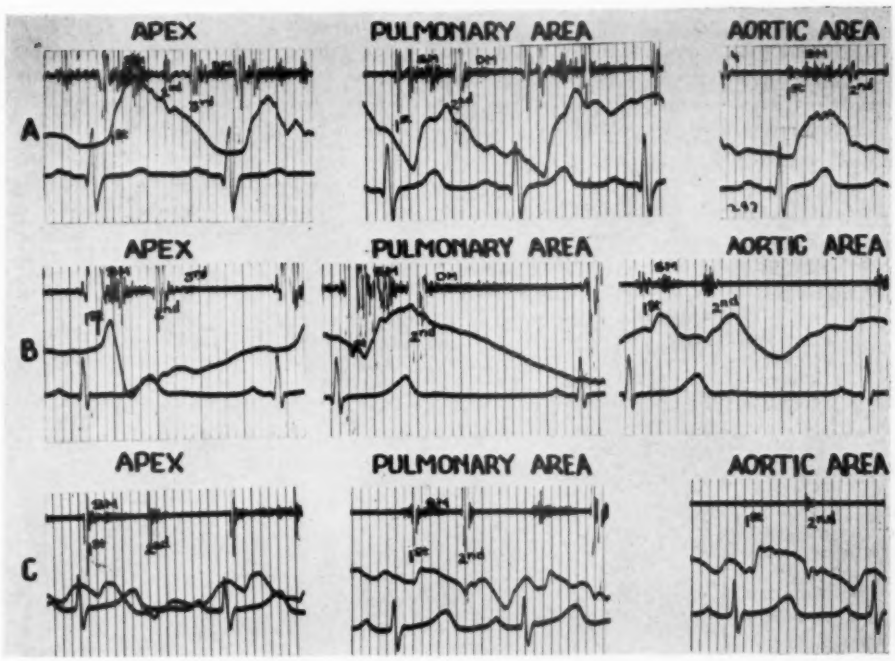


Fig. 3, *A*, *B*, and *C* (Case 1).—*A*, Preoperative phonocardiogram indicating a loud third heart sound followed by a diastolic murmur at the apex and an early diastolic murmur at the pulmonic area. Note the prominent systolic murmur recorded in the aortic area as well as over the pulmonic area and at the apex. *B*, Phonocardiogram taken fifteen days after operation with maximal amplification. The systolic murmur and third heart sound at the apex are less intense, the apical diastolic murmur has disappeared, and the early diastolic murmur at the pulmonic area is barely discernible. *C*, Phonocardiogram four months after operation. No diastolic murmurs are recorded and the systolic murmur has been reduced to Grade 1 intensity.

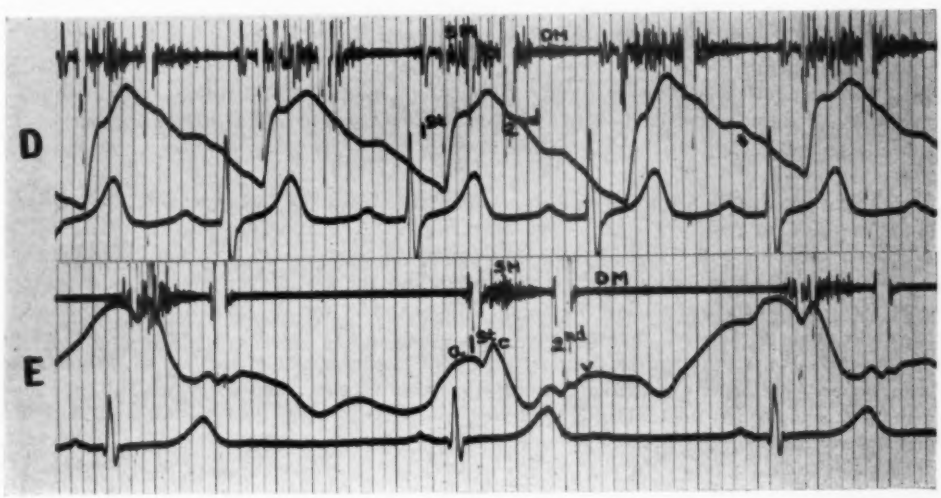


Fig. 3, *D* and *E*.—*D*, Preoperative phonocardiogram at the pulmonic area, with some complexes suggesting a continuous murmur. *E*, Phonocardiogram at the pulmonic area fifteen days after operation. The diastolic murmur is now barely detectable (better seen in *B*).

At the termination of these studies, the diagnosis still remained in doubt. On clinical grounds patent ductus was suspected, but the lack of a typical murmur and the normal pulse pressure were against this diagnosis. From an x-ray standpoint, an atrial septal defect, a large ventricular septal defect, or a communication between aorta and pulmonary artery were considered. The marked enlargement of the pulmonary artery and its branches and the size and configuration of the heart seemed most suggestive of atrial septal defect. Phonocardiograms were as inconclusive as clinical auscultation had been. The electrocardiogram showed no diagnostic changes but was evidence against atrial septal defect because of the lack of definite right ventricular preponderance. The catheterization studies were consistent with a large patent ductus (or other communication between the aorta and pulmonary artery) together with pulmonary regurgitation. The data could also be explained by a high ventricular septal defect, with or without patent ductus.

TABLE I. CARDIAC CATHETERIZATION DATA—CASE 1

LOCATION	PRESSURE (MM. Hg)	O_2 (VOLUME PER CENT)	O_2 (PER CENT SATURATION)
Right pulmonary artery	± 110/50	13.0	90
Main pulmonary artery	± 110/50	13.7	95
High right ventricle	± 90/0	13.2	92
Mid-right ventricle	± 90/0	12.2	85
Low right ventricle (by fluoroscopic observation)		10.3	72
Low right auricle	± 15/2	10.8	75
Mid-right auricle	± 15/2	9.8	68
Superior vena cava		9.0	62
Femoral artery		14.2	98

O_2 capacity 14.4 volume per cent.

Despite the uncertainty of the diagnosis, surgical intervention was undertaken in the hope that a correctable shunt between aorta and pulmonary artery might be found. Upon exposure of the great vessels, the thrill was readily palpable in an abnormally tense pulmonary artery. A large patent ductus, equal in diameter to the aorta and about 1 cm. in length, was found. It was successfully ligated, and the tension in the pulmonary artery was considerably reduced and the thrill abolished.

The postoperative course was uneventful. Fig. 3,*B* illustrates the change in the phonocardiograms taken fifteen days after operation. The systolic murmur could still be recorded but only with maximal amplification. The third heart sound was less intense; the apical diastolic murmur had disappeared, and the early high-pitched diastolic murmur at the pulmonary area was barely detectable.

The patient was last seen four months after operation. He had been well and active. Examination revealed no evidence of congestive heart failure. The heart was slightly enlarged. The pulmonary second sound was still accentuated, although considerably less than it had been prior to operation. The systolic thrill had disappeared, and the systolic murmur at the base of the heart was reduced to Grade 1 intensity (Fig. 3,*C*). An electrocardiogram (Fig. 1,*B*) showed no diagnostic change from the preoperative record, although the T wave in Lead aV_L had become low upright. X-ray examination demonstrated decrease in the size of the pulmonary artery and its branches. The heart was smaller in total transverse diameter, but there was still prominence in the region of the left ventricle (Fig. 2,*C*).

CASE 2.—This 5-year-old girl was admitted to the hospital on Jan. 24, 1949. The child's mother had had German measles during the second month of pregnancy. Delivery was normal and considered to be full term inasmuch as the birth weight of 4 pounds and 3 ounces was in keeping with the unusually small stature of the patient's parents. Strabismus and bilateral cataracts were noted at birth. A harsh systolic murmur was first detected during hospitalization for treatment

of the eye defects at the age of 1 year. The murmur was variously described as being maximal at the apex or at the fourth and fifth left intercostal spaces with wide transmission over the precordium. Growth and development were much retarded. No cardiac symptoms were noted; however, her activity had always been limited by poor vision.

The patient was strikingly small for 5 years. Her weight was that of a normal 1½-year-old; her height was consistent with an age of 2½ years. Convergent strabismus and a cataract of the right eye were obvious. There was no cyanosis or clubbing. Examination of the neck showed no venous distention, but prominent arterial pulsations were seen. The blood pressure was 90/75 mm. Hg; the pulse was 100 per minute and regular. The heart was moderately enlarged to the left. A systolic thrill was palpable over the upper precordium and in the suprasternal notch.

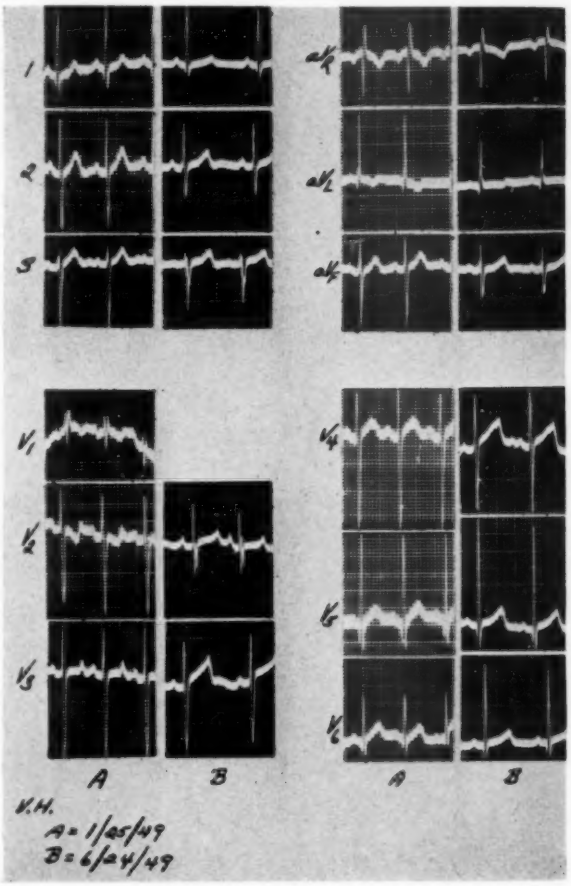
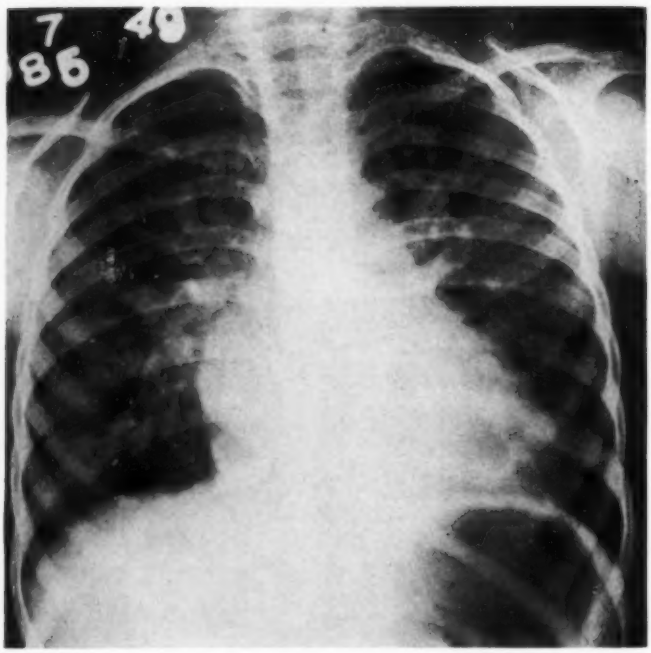


Fig. 4 (Case 2).—*A*, Preoperative electrocardiogram. The high voltage of R in Leads V_5 and aV_L with inverted T wave in Lead aV_L suggests left ventricular hypertrophy. *B*, Electrocardiogram taken five months after operation with lower R and upright T in Lead aV_L.

There was a Grade 3 to 4 harsh systolic murmur maximal in the second and third intercostal spaces both to the right and left of the sternal border and in the suprasternal notch. This murmur was widely transmitted over the entire precordium, neck, shoulders, and posterior chest. Following a much accentuated pulmonic second sound was a Grade 2 early, high-pitched, decrescendo diastolic murmur best heard at the pulmonic area and along the left sternal border. At no time was there a clearly defined continuous murmur typical of a patent ductus arteriosus, but there



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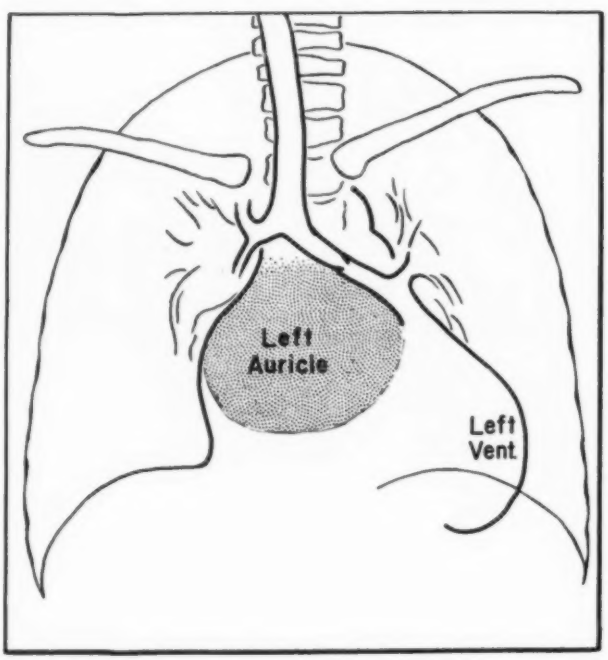
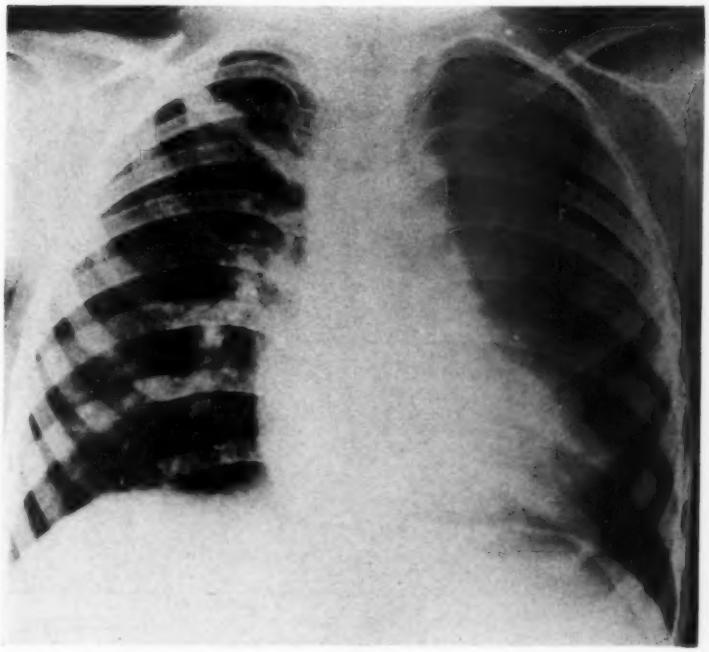
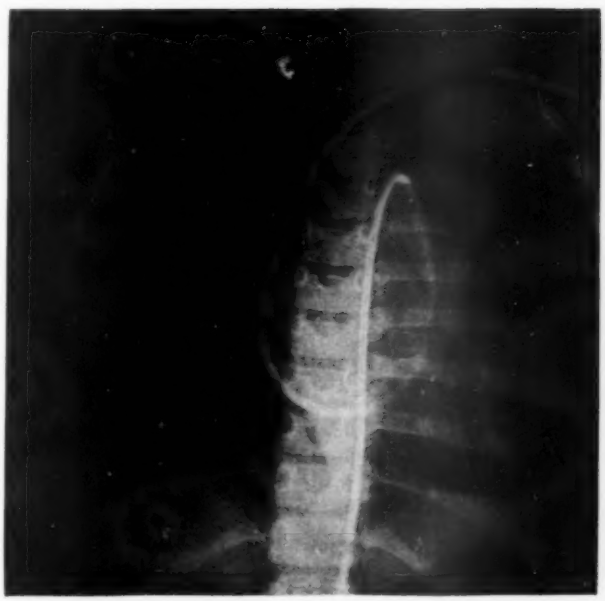


B.

Fig. 5, *A* and *B* (Case 2).—*A*, Preoperative roentgenogram showing cardiac enlargement and prominent hilar vascular shadows. *B*, Line drawing of *A*, indicating the appearance of the large left auricle as seen through the heart shadow.

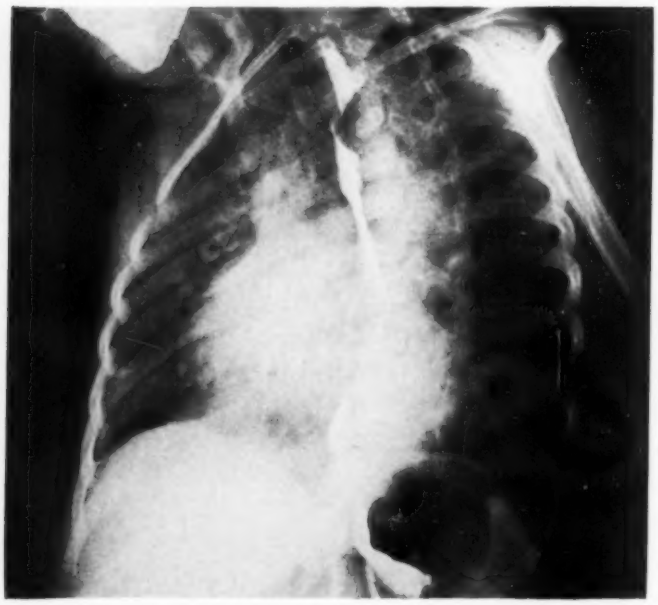


C.

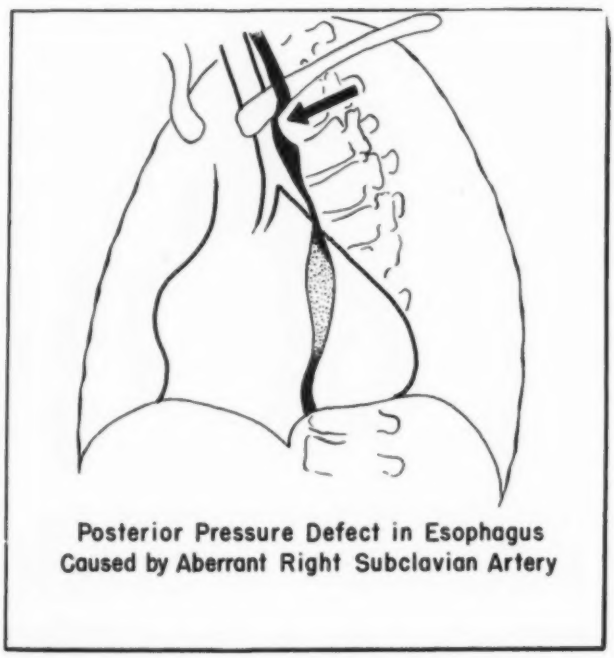


D.

Fig. 5, *C* and *D*.—*C*, Roentgenogram taken two and one-half months after operation. *D*, Portable film showing catheter passing through the ductus and lying in the aorta.



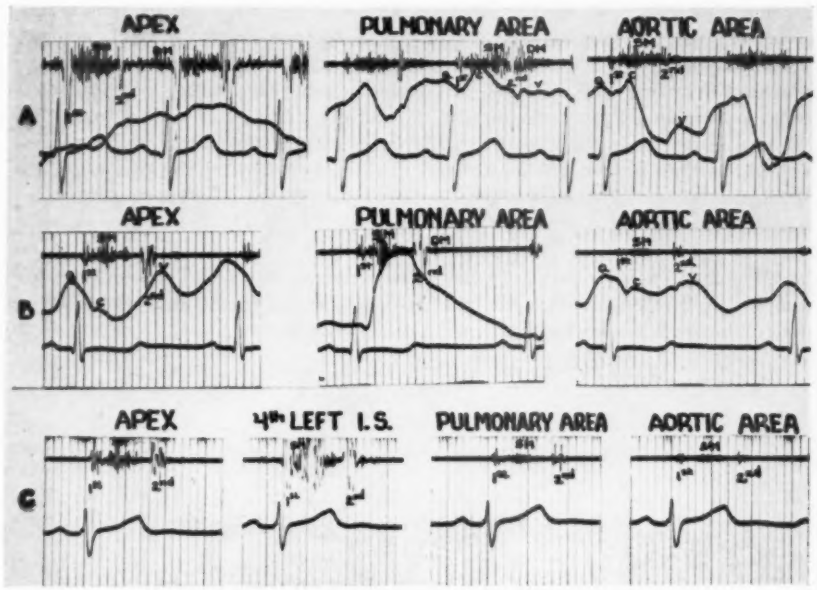
E.



F.

Fig. 5, *E* and *F*.—*E*, Left anterior oblique roentgenogram demonstrating the aberrant right subclavian artery. *F*, Line drawing of *E*.

was occasionally the suggestion of an indistinct machinery murmur underlying the high-pitched early diastolic murmur. A short mid-diastolic murmur was present at the apex. Arterial pulsations were normal in the lower extremities. There was no hepatic enlargement or peripheral edema.



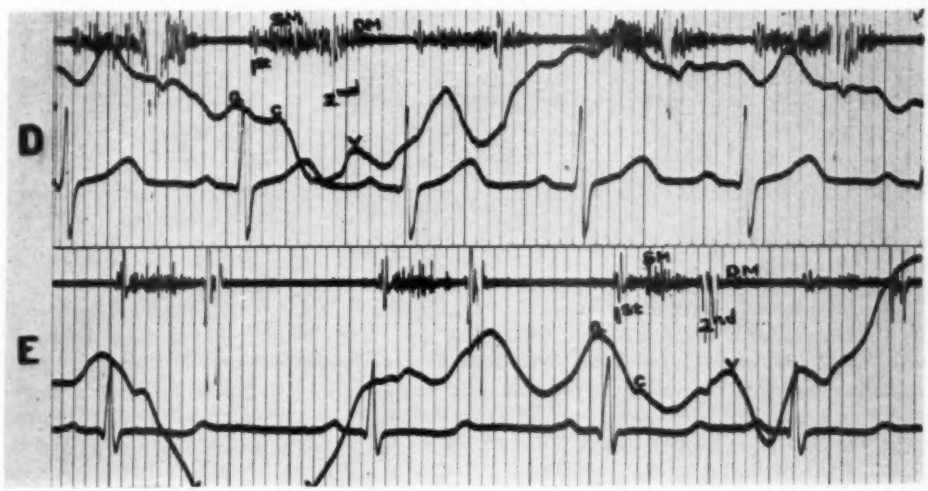


Fig. 6 (Case 2).—*A*, Preoperative phonocardiogram showing systolic and diastolic murmurs at the apex and base. *B*, Tracing taken fifteen days after operation. A third heart sound is recorded at the apex. The systolic murmur has diminished in intensity and an early diastolic murmur at the pulmonic area is minimal. *C*, Tracing taken two and one-half months after operation. A systolic murmur of moderate intensity is still present at the apex and base, but is maximal at the fourth left interspace. *D*, Tracing taken at the pulmonic area preoperatively. In the first, fourth, and fifth complexes the diastolic murmur is more intense and suggests continuation with the systolic murmur. *E*, Tracing taken at the pulmonic area fifteen days after operation, showing the persistence of the systolic murmur but with a minimal diastolic murmur immediately following the second sound.

An electrocardiogram (Fig. 4,*A*) showed moderate left axis deviation, an inverted T wave in Lead aV_L, and rather high voltage of R waves in Lead V_5 suggestive of left ventricular hypertrophy. X-ray examination (Fig. 5,*A*) showed enlargement of the heart in the region of both ventricles and the left auricle. The hilar and pulmonary vascular shadows were moderately increased in size. Fluoroscopically, the hilar arterial shadows showed pulsations of moderately increased amplitude. Barium in the esophagus demonstrated an aberrant right subclavian artery (Fig. 5,*E*).

A phonocardiogram (Fig. 6,*A* and *D*) at the apex recorded a systolic murmur and a diastolic murmur beginning a short interval after the second sound. The tracing taken in the pulmonary area showed a systolic murmur with maximum intensity at times in mid-systole, while at other times the murmur reached a peak in late systole and was more suggestive of a continuous murmur.

A cardiac catheterization was performed (Table II). During the procedure the catheter passed through a communication between the bifurcation of the pulmonary artery and the aorta and was advanced until its tip lay below the diaphragm (Fig. 5,*D*). It was then possible to record continuous pressures as the catheter was again withdrawn into the main pulmonary artery. A considerable difference in systolic pressures existed between the aorta and pulmonary artery. However, there was little or no diastolic pressure gradient between these two vessels. On the basis of the cardiac catheterization findings, operation was advised.

TABLE II. CARDIAC CATHETERIZATION DATA—CASE 2

LOCATION	PRESSURE (MM. Hg)	O_2 (VOLUME PER CENT)	O_2 (PER CENT SATURATION)
Right pulmonary artery	75–80/50 (Mean 65)	13.7	88
Aorta	110–120/50 (Mean 88)	15.4	99
Main pulmonary artery	65–80/35 (Mean 60)	15.0	96
Mid-right ventricle	65/0 (Mean 30)	9.9	64
Right auricle	± 0	9.8	63
Superior vena cava		9.0	61

O_2 capacity 15.6 volume per cent.

At the time of thoracotomy a coarse thrill was palpable along a tense pulmonary artery which was about two-thirds the size of the aorta. The ductus was readily demonstrated beneath the aortic arch and was estimated to be about 1.0 cm. in length and 0.8 cm. in diameter. The left subclavian artery was unusually large and gave rise to a branch that passed posterior to the esophagus, presumably the aberrant subclavian artery noted on x-ray examination. After ligation of the ductus, the pulmonary artery was softer, although a coarse thrill, much diminished in intensity, was still present in that vessel and in the aorta. A biopsy was taken from the left upper lobe of the lung. A striking feature of the specimen was marked dilatation and mild intimal proliferation of the pulmonary arterioles. The alveolar walls were thickened but there was no edema evident.

The postoperative course was uneventful. Fig. 6,*B* illustrates the change in the phonocardiograms taken fifteen days after operation. In the apical phonocardiogram a third heart sound was recorded. Although a systolic murmur was still present at the apex and at the pulmonic area, it was of much diminished intensity, and the diastolic murmur had almost disappeared.

The patient returned for follow-up study two and one-half and again five months after operation. She had been entirely well and fairly active. On examination there was no evidence of con-

gestive heart failure. The heart was not enlarged to percussion. A Grade 3 systolic murmur, loudest at the lower left sternal border, was still heard, but the systolic thrill had disappeared and no diastolic murmurs were audible. The electrocardiogram (Fig. 4,*B*) showed no diagnostic change from the preoperative tracing, although the T wave in Lead aV_L had become less inverted. X-ray examination (Fig. 5,*C*) demonstrated a marked decrease in the size of the pulmonary artery and its branches, and the heart appeared smaller than in the preoperative films. A phonocardiogram (Fig. 6,*C*) confirmed the persistence of a systolic murmur which to auscultation was loudest just to the left of the lower sternal border in the fourth intercostal space.

DISCUSSION

The two cases of patent ductus here reported are exceptional in that cardiac catheterization was essential in establishing the diagnosis. In the great majority of cases the correct diagnosis is clear following clinical studies which usually reveal a continuous murmur in the pulmonic area, wide pulse pressure, slight enlargement of the heart and pulmonary vessels on x-ray examination, and a normal electrocardiogram. Under such circumstances, cardiac catheterization studies are not needed to confirm the diagnosis. In a typical case of patent ductus, both systolic and diastolic pressures are higher in the aorta than corresponding pressures within the pulmonary artery. There occurs, therefore, a continuous flow through the ductus. Because of the high output from the left ventricle, a normal systolic pressure is maintained in the systemic circulation, but because of diastolic leakage through the ductus, the systemic diastolic pressure is reduced. The systemic pulse pressure is consequently increased, much as in a case of free aortic regurgitation. In the two atypical cases reported in this paper, the data obtained by cardiac catheterization offered a reasonable explanation for the lack of a continuous machinery murmur. A marked elevation of the pulmonary diastolic pressure was observed in both patients. In the second patient, in whom direct measurement of the intra-aortic pressure was possible, the diastolic pressure in the pulmonary artery approximated that in the systemic circuit, so that minimal flow from aorta to pulmonary artery through the ductus during diastole would be expected. Not only the absence of a murmur with definite continuation into diastole is explicable on this basis, but the absence of a high systemic pulse pressure as well.

At the time of measurement of the aortic pressures in the second patient, the ductus was partially occluded by the cardiac catheter which had passed through it. This would tend to result in a measured pressure in the aorta higher than the true pressure. However, in neither of the two cases studied was there evidence of a right-to-left shunt through the ductus since the arterial oxygen saturation was normal in both patients.

Aside from the lack of a definite continuous murmur and wide pulse pressure, the other physical findings in these children were of interest and importance. The loud pulmonary second sound followed by an early, high-pitched diastolic murmur was consistent with pulmonary hypertension and functional pulmonary regurgitation. Pulmonary regurgitation may explain the high oxygen content of blood samples taken from the right ventricle in the first patient. The slight mid-diastolic murmur at the apex which was demonstrated in our patients would be consistent with the presence of a dilated left ventricle ("relative mitral stenosis").

A part of the very loud systolic murmur and systolic thrill, which were unusual in that they were present not only to the left of the sternum but in the aortic valve area and neck as well, may have been due to a high left ventricular output into a dilated ascending aorta ("relative aortic stenosis"). Additional associated defects cannot be excluded in either of these two cases despite the disappearance of the systolic thrill and diminution of the systolic murmurs at the time of follow-up examination. It is quite clear that the ductus was complicated by an additional congenital lesion in the second patient, perhaps by a ventricular septal defect or by subaortic stenosis.

The electrocardiograms of these patients both showed an inverted T in Lead aV_L which tended to become upright after operation. In the presence of an upright P wave and a left ventricular QRS complex in this lead, such changes would be consistent with the presence of left ventricular strain alleviated by the operation. The presence of left ventricular hypertrophy in both patients was suggested by the tall R waves in the unipolar chest leads taken over the left ventricle. In the first patient there was a tendency to right axis deviation, and the tall R waves in the chest leads taken over the right ventricle pointed to right ventricular hypertrophy. Such a finding is most unusual in the presence of uncomplicated patent ductus arteriosus, but it may be related to the extreme pulmonary hypertension in this case.

It has been pointed out that many of the atypical cases of patent ductus are found in infancy or early childhood and only with the passage of time does the clinical picture become obvious. It may be of great importance to establish a correct diagnosis early, however, so that surgical correction can be carried out before congestive heart failure or irreversible vascular changes occur in the lungs.[6] This is particularly true when there is a communication of large size between the aorta and pulmonary artery as in the two cases cited above. In the second of these cases, lung biopsy demonstrated definite vascular abnormalities, and in both notable cardiac enlargement had occurred.

SUMMARY AND CONCLUSIONS

1. Two patients (a boy aged 6 years and a girl aged 5 years) with patent ductus arteriosus, in whom the clinical diagnosis was not clear because of the absence of a continuous machinery murmur, were studied by cardiac catheterization.

2. In one of the patients, passage of the catheter through the ductus and down the aorta permitted direct pressure measurements in that vessel for comparison with those in the pulmonary artery.

3. The finding of a markedly elevated diastolic pressure in the pulmonary circuit approaching that of the systemic diastolic pressure is suggested as an explanation for the absence of the typical continuous murmur. Under these circumstances diastolic flow through the ductus is minimal.

4. In both patients a large patent ductus arteriosus was found and successfully ligated at operation.

We wish to express our gratitude to Dr. Addison L. Messer and Dr. Timothy B. Counihan for recording and interpreting the phonocardiograms and to Miss Ann Murphy for her technical assistance in carrying out the gas analyses in this study.

ADDENDUM

Since the above cases were reported, we have studied a third patient with similar clinical and physiological findings. This was a 6-year-old boy with a known heart murmur since 4 months of age. There was a history of maternal rubella during the first month of pregnancy, and the patient had been born with a congenital cataract of the left eye. Growth and weight gain had been slow. He had been digitalized at 2 years of age because of congestive failure complicating pneumonia and maintained on the drug since. There had never been cyanosis or limitation of activity. Physical examination revealed a poorly developed and poorly nourished boy. The neck veins were slightly distended and pulsating with the patient in the upright position. The heart was markedly enlarged with the apex impulse in the sixth intercostal space in the anterior axillary line. A Grade 4 to 5 harsh systolic murmur and readily palpable thrill were most prominent in the suprasternal notch and pulmonic area, but the murmur was widely transmitted over the entire chest. The pulmonic second sound was greatly accentuated. A Grade 2, early, high-pitched diastolic blow along the left sternal border and a Grade 2 apical mid-diastolic rumble were also noted. No continuous machinery murmur could be detected. The blood pressure was 125/30 mm. Hg. There was no cyanosis or clubbing. A hemoglobin was 13.1 Gm. per cent. X-ray and fluoroscopic examinations showed generalized cardiac enlargement and a great increase in the size of the pulmonary vascular markings. The descending aorta was seen to the left of the spine. An electrocardiogram indicated right and left ventricular hypertrophy and digitalis effect. Cardiac catheterization demonstrated a large left-to-right shunt into the pulmonary artery where blood samples were 86 to 89 per cent saturated with oxygen. In contrast, samples obtained from the right ventricle, right auricle, and superior vena cava were between 54 and 60 per cent saturated. The pressure in the pulmonary artery was 80/50 mm. Hg; that recorded simultaneously from the radial artery was 100/48 mm. Hg. The radial and femoral arterial oxygen saturations were 94 and 99 per cent and were considered evidence against significant right-to-left shunt. At operation it was found that instead of a patent ductus arteriosus there was fusion between the ascending arch of the aorta and the main pulmonary artery. Although the distal point of fusion could be visualized, the vessels appeared to have a joint course without clear evidence of a division between them proximally, even after opening the pericardium. It was therefore deemed technically impossible to close the abnormal communication. The patient had an uneventful postoperative course and was discharged from the hospital with the condition unchanged.

We believe that preoperative Diodrast studies might have indicated the true nature of the defect which appeared to be an aortic septal defect with extensive fusion of pulmonary artery and ascending aorta, indistinguishable by clinical and cardiac catheterization studies from a large patent ductus arteriosus.

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FACTORS REGULATING PULMONARY "CAPILLARY" PRESSURE IN MITRAL STENOSIS. IV.

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Bland and Sweet[1] have called attention to the small, but important, group of rheumatic patients who have "tight" mitral stenosis. These patients are particularly prone to recurrent bouts of severe pulmonary edema, often without known cause. Interest in this problem was awakened by the random occurrence of pulmonary edema during cardiac catheterization of patients with mitral stenosis.[2,3] Why did some patients develop pulmonary edema on exercise and others not? Why were some individuals in pulmonary edema even at rest and others not, although the clinically judged and physiologically calculated[4] "degree of mitral stenosis" may have been the same in these patients?

This report will be concerned with the utilization and interpretation of data already presented elsewhere in order to define those factors which result in recurrent pulmonary edema in this disease.

METHODS

On the day of study, the patients fasted or else received a light breakfast of orange juice, toast, jam, and black coffee. Cardiac catheterization was performed in the usual fashion. Pulmonary "capillary" pressure[5] was recorded at rest (after five minutes or more, during which time pulse and respiration had become stable) and in some of the studies again during exercise (at the second minute of a three-minute period of exercise as described later). Sufficient time was allowed between exercise periods to allow pulse and respiration to return to normal, usually ten minutes or more.

The catheter was then withdrawn to a point just distal to the bifurcation of the pulmonary artery. A No. 20 or 21 short-bevel needle was inserted into the brachial artery, the lumen of which was kept patent by a slow intra-arterial saline solution infusion. After pulse and respiration had returned to the initial resting level, a resting cardiac output was measured by the direct Fick method. Expired air was collected for three minutes in a Douglas bag, and blood samples

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were withdrawn simultaneously from the brachial artery and pulmonary artery midway during the gas collection. Immediately thereafter, pressures in the pulmonary and brachial arteries were recorded. In those patients who were exercised, pressures were taken after two minutes of exercise. Expired air was collected between 2.5 and 3.0 minutes. Midway during the collection of the expired air, blood samples were withdrawn from the pulmonary and systemic arteries simultaneously. The volume of expired air was measured in a Tissot spirometer, and the concentration of oxygen alone was measured by a Pauling oxygen analyzer. From previous studies[6] of Haldane analysis of expired air, mean correction factors of 1.007 and 1.01 were derived for converting expired volume to inspired volume under resting conditions and during exercise, respectively. Blood samples were analyzed for oxygen content, capacity, and saturation by the method of Van Slyke and Neill[7] and the arteriovenous oxygen difference calculated.

Pressures were measured with Hamilton manometers[8] or, in the latter part of the series, with electromanometers*[9] which recorded on a multi-channel, direct-writing oscillograph. The recording was calibrated with a mercury manometer after each pressure tracing. The zero point for all pressures was 10 cm. anterior to the back with the patient recumbent. A saline manometer was used for checking mean pressures but not for analytical purposes. Mean pressures were obtained by planimetric integration of the pressure tracings obtained from the Hamilton manometer and by electrical integration of the oscillographic tracings.

Exercise was performed with the patient recumbent, pedalling a bicycle at the rate of 56 r.p.m. timed with a metronome.

Pulmonary arteriolar (PAR) and total pulmonary (TPR) resistances[2] were calculated from the Poiseuille equation, $\text{Resistance} = \frac{\text{Pressure gradient}}{\text{Rate of blood flow}}$, as follows:

$$\text{PAR} = \frac{\text{PA}_m - \text{“PC}_m\text{”}}{\text{CO}} \times 1{,}332 \text{ dynes seconds cm.}^{-5}$$

$$\text{TPR} = \frac{\text{PA}_m}{\text{CO}} \times 1{,}332 \text{ dynes seconds cm.}^{-5}$$

where PA_m = pulmonary arterial mean pressure in mm. Hg
$\text{“PC}_m\text{”}$ = pulmonary “capillary” mean pressure in mm. Hg
CO = cardiac output in c.c. per second
1,332 = factor to convert mm. Hg to dynes per cm.^{2}

The mitral valve cross-sectional area (MVA) in cm.^{2} was calculated as described elsewhere[4] from the following formula:

$$\text{MVA} = \frac{\text{MVF}}{31\sqrt{\text{“PC”} - 5}}$$

*Sanborn Company, Cambridge, Mass.

where MVF = mitral valve flow rate in c.c. per diastolic second
31 = empirical constant
"PC" = pulmonary "capillary" pressure in mm. Hg, as an index of left atrial mean pressure
5 = assumed left ventricular diastolic pressure in mm. Hg

GENERAL PRINCIPLES

The occurrence of clinical pulmonary edema has been consistently associated with elevations of pulmonary "capillary" pressure above the colloid osmotic pressure of plasma. Pulmonary "capillary" pressure was elevated to 35 mm. Hg or more, as measured from the zero point used in this laboratory, in all patients who developed pulmonary edema during cardiac catheterization, including those who had diseases other than mitral stenosis.

In this discussion, no attempt is made to define the exact level of pulmonary "capillary" pressure or the duration of elevation of pressure necessary to produce pulmonary edema. We are primarily interested in the various factors responsible for rises in pulmonary "capillary" pressure in patients with mitral stenosis, since these factors initiate the train of events leading to pulmonary transudation and the production of pulmonary symptoms. The presence of pulmonary edema was denoted by the development of râles, cough, and orthopnea, and often by frothy sputum.

In this study, pulmonary "capillary" pressure is used as an index of both left atrial pressure[10] and true pulmonary capillary pressure, although this pressure is believed to be a few millimeters of mercury less than the true capillary pressure.[5] As such an index, pulmonary "capillary" pressure is employed in the hydraulic formula for calculating the area of the mitral valve orifice.[4] The pressure head, as measured in the pulmonary "capillaries" and left atrium, is converted to velocity or kinetic energy in order to drive blood through the mitral valve orifice. In so doing, this pressure may exceed the colloid osmotic pressure of plasma and cause transudation in the pulmonary capillary bed. The smaller the valve orifice, the more pressure head is needed to maintain a given flow, and the greater the given flow, the faster this flow must be per unit of time, and so even more pressure head is required. The effects of valve area and valve flow on the required pressure head may be expressed by solving the orifice formula for pulmonary "capillary" pressure ("PC") as follows:

$$\text{"PC"} = \frac{\text{MVF}^2}{31^2 \times \text{MVA}^2} + 5$$

Thus, pulmonary "capillary" pressure, an index of left atrial pressure, must rise directly as the square of the mitral valve flow rate (MVF) and inversely as the square of the mitral valve area (MVA). Because the mitral valve area is fixed in each patient, the moment-to-moment level of pulmonary "capillary" pressure will vary directly as the square of the required valvular flow rate. Actually, the flow rate depends on the pressure head, and, unless pressure builds up to the required level, the increase in flow rate cannot occur. Under most conditions, bodily demands for blood are met, and pressure rises to deliver the blood through the stenotic orifice. An elucidation of the factors which demand

an increased rate of flow through the valve will indicate under what conditions pressure in the left atrium and pulmonary "capillaries" must rise.

The interrelation of factors is shown in Fig. 1. As stated above, mitral valve flow (II) and mitral valve area (III) affect the level of pulmonary "capillary" pressure (I). The rate of flow of blood through the mitral valve depends on the amount of blood that must be delivered to the tissues, i.e., cardiac output (A), and the amount of time during which the valve is open for passage of that amount of blood. Blood flows through the mitral valve only during that fraction of a minute when the ventricle is in diastole, and in mitral stenosis the

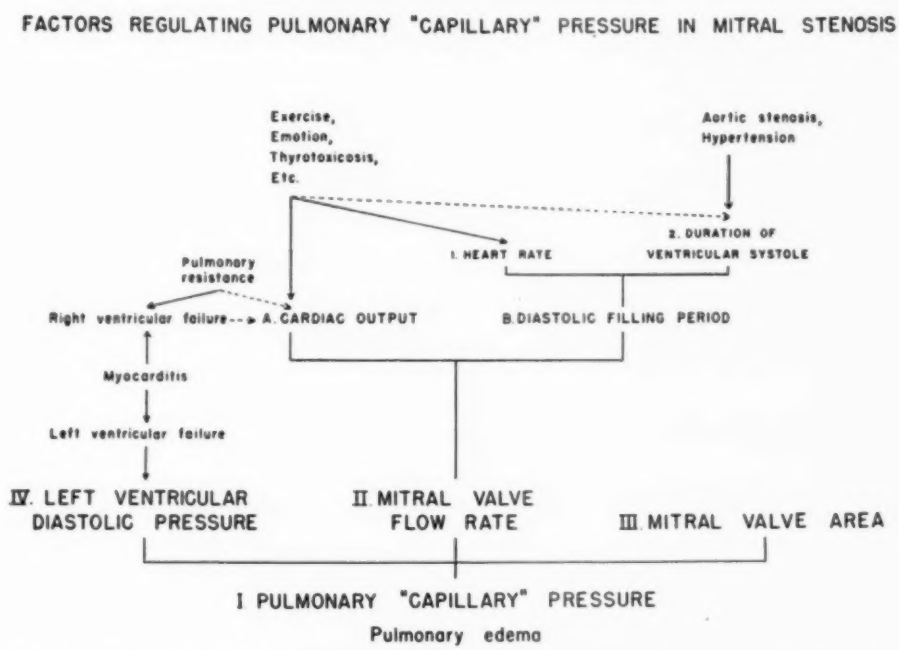

Fig. 1.—The various factors regulating pulmonary "capillary" pressure are numbered in the same order as they are mentioned in the text under General Principles, Observations, and Discussion. The effect of various clinical and pathological states on the factors is illustrated as follows: Solid lines indicate that an increase and broken lines indicate that a decrease in pulmonary "capillary" pressure is caused by the particular condition.

entire period of diastole is presumably utilized for blood flow.[11] This period is called the diastolic filling period per minute (B). This is obtained by multiplying the heart rate per minute by the diastolic filling period per beat (dfp). This period is measured directly on brachial arterial and, occasionally, on pulmonary arterial tracings.[4] The duration of ventricular diastole is believed to be passive and is dependent on (1) the heart rate and (2) the duration of ventricular systole. Increases in these two factors decrease the diastolic filling period. Valve flow rate, then, is increased in response to increases in cardiac output, heart rate, and the duration of ventricular systole.

Thus, clinical conditions which are known to increase cardiac output or to cause tachycardia, such as exercise,[3,12] emotion,[13,14,15] thyrotoxicosis,[16,17] and

TABLE I. RESTING PHYSIOLOGIC DATA IN PATIENTS WITH MITRAL STENOSIS

PATIENT	MITRAL VALVE AREA (CM.²)	PULMONARY EDEMA	PULMONARY "CAPILLARY" PRESSURE (MM. Hg)	MITRAL VALVE FLOW (C.C. PER DIASTOLIC SECOND)	DIASTOLIC FILLING PERIOD (SECONDS PER BEAT)	PULSE RATE (PER MINUTE)	DIASTOLIC FILLING PERIOD (SECONDS PER MINUTE)	CARDIAC OUTPUT (LITERS PER MINUTE)	RESISTANCE (DYNES SECONDS CM.⁻⁵)	
									PULMONARY ARTERIOLAR	TOTAL PULMONARY
J. D.	2.5	0	19	303	0.31	100	31	9.4	51	212
J. F.	1.6	0	21	192	0.47	72	34	6.5	135	394
L. B.	1.4	0	20	172	0.31	90	28	4.8	67	400
L. C.	1.4	0	27	200	0.25*	106	27	5.4	711	1110
J. M.	1.3	0	25	176	0.23*	107	25	4.4†	145	600
Gr.	1.1	+	32	175	0.40	100	40	7.0	114	480
Gr.	1.0	+	38	175	0.23*	120	27	4.7†	221	866
Ba.	0.9	0	32	148	0.33	105	35	5.2	569	1062
L. T.	0.9	0	24	122	0.52	70	36	4.4	382	820
R. C.	0.9	+	39	156	0.31	108	34	5.3	544	1130
M. B.	0.8	0	17	84	0.40	96	38	3.2	150	574
M. T.	0.7	0	21	91	0.44*	79	35	3.2	225	750
E. S.	0.7	0	26	98	0.50	80	40	3.9	451	984
E. S.	0.7	0	28	89	0.44	84	37	3.3	242	921
E. D.	0.6	+	36	109	0.23	140	32	3.5	411	1235
M. G.	0.6	0	30	90	0.36*	82	30	2.7†	1480	2372
McL.	0.6	+	54	127	0.32	105	33	4.2	762	1790
R. W.	0.6	0	34	95	0.49	75	37	3.5	274	1050
N. L.	0.6	0	28	84	0.36	105	38	3.2	950	1650
W. F.	0.5	0	23	65	0.50	80	40	2.6	1139	1845
D. K.	0.5	+	46	96	0.13	204	26	2.5†	256	1730
M. M.	0.4	0	22	54	0.77	56	43	2.3	1150	1915
D. V.	0.4	+	35	75	0.40	100	40	3.0	746	1680

*Measured on pulmonary arterial tracing.
†Benedict-Roth method used for oxygen consumption.

anemia,[18,19,20] should often lead to bouts of pulmonary edema in patients with mitral stenosis (Fig. 1).

The final factor which may affect pulmonary "capillary" pressure is left ventricular diastolic pressure (IV). In the presence of ventricular incompetency, either in the face of an excessive work load or a poorly functioning myocardium, the diastolic filling pressure rises, and there will occur an equal rise in pulmonary "capillary" pressure to maintain blood flow.

OBSERVATIONS AT REST

Pertinent data on the twenty-one patients are presented in Table I. Further details of the circulatory dynamics of these same subjects will be found in Table I of a preceding communication.[2]

I. Pulmonary Edema and Pulmonary "Capillary" Pressure.—Six patients (R. C., Gr. two times, D. K., D. V., McL., E. D.) developed pulmonary edema during studies at rest. Pulmonary "capillary" pressure in these six ranged from 32 to 54 mm. Hg, while the highest pulmonary "capillary" pressure recorded in the patients not in clinical pulmonary edema was 34 mm. Hg.

II. Mitral Valve Flow.—The rate of flow of blood through the mitral valve in each of the six patients was at a level which required a large pressure gradient (or "head") across the mitral valve with an elevation of left atrial and pulmonary "capillary" pressure to 32 mm. Hg or more. This pressure rise was related to the degree of stenosis as well as to the rate of flow.

The rate of flow depends on the required cardiac output and the duration of the left ventricular diastolic filling period.

A. Cardiac output: In patients R. C. and Gr., cardiac outputs were normal or increased at the time of study. Normal or increased outputs did not occur in any other patients with mitral stenosis of 1 cm.^{2} or less.

B. Diastolic filling period: The duration of ventricular diastole, the period during which blood flows through the mitral valve, was less than normal in all six patients because the heart rate was 100 or greater. By comparison, in only two of ten individuals with similar degrees of stenosis who were not in pulmonary edema was the rate 100 or more.

III. Mitral Valve Area.—All six patients had mitral valve areas of 1 cm.^{2} or less, although ten of the fifteen patients not in pulmonary edema had similar degrees of stenosis. Because of the severe stenosis, the rises in pressure for a given flow were excessive.

The interrelationship between these various factors affecting pulmonary "capillary" pressure at rest is best illustrated by examples. In patient R. C., with a mitral valve area of 0.9 cm.^{2}, cardiac output was normal and the pulse rate slightly elevated. As a result, the flow rate was 156 c.c. per diastolic second, the normal being 150 to 300 c.c. per diastolic second (Fig. 2), and left atrial and pulmonary "capillary" pressures rose to 39 mm. Hg, the normal being 9 mm. Hg,[21] to maintain such a rate of flow. Mathematically, this is shown as follows:

$$\text{MVF} = \text{MVA} \times 31\sqrt{\text{"PC"} - 5}$$

$$\text{156 c.c. per diastolic second} = 0.9\ \text{cm.}^2 \times 31\sqrt{39 - 5}$$

In patient D. K., on the other hand, with a mitral valve area of 0.5 cm.², the heart rate of 204 decreased the diastolic filling period from a normal of about 0.4 to 0.5 second per beat to 0.13 second per beat. The mitral valve flow rate was only 96 c.c. per diastolic second, less than two-thirds of the normal flow rate (Fig. 2). Pulmonary edema ensued because pulmonary "capillary" pressure had to be 46 mm. Hg to maintain that rate of flow in the presence of severe stenosis. Mathematically, this is shown as follows:

$$\text{MVF} = \text{MVA} \times 31\sqrt{\text{"PC"} - 5}$$

$$96 \text{ c.c. per diastolic second} = 0.5 \text{ cm.}^2 \times 31\sqrt{46 - 5}$$

THE INTERRELATIONSHIPS OF CARDIAC OUTPUT,
PULSE RATE AND MITRAL VALVULAR FLOW RATES

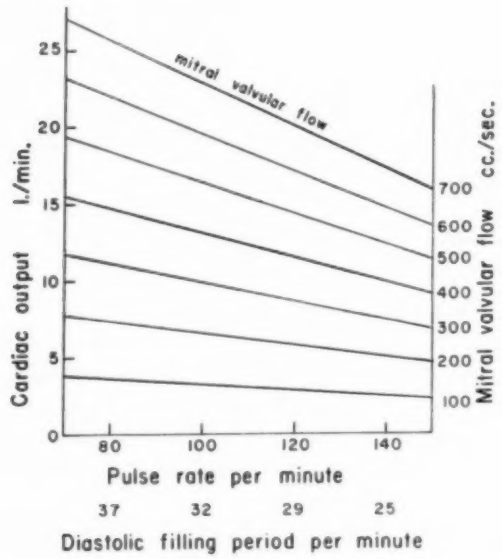

Fig. 2.—In this nomogram, mitral valve flow, cardiac output, pulse rate, and diastolic filling period are approximately interrelated. The cardiac output may be calculated at a given valve flow and heart rate, or the rate of flow across the mitral valve may be calculated at a given level of cardiac output and pulse rate.

Five patients had valvular areas of about 0.6 cm.² Two (E. D. and McL.) has valvular flow rates of 109 and 127 c.c. per diastolic second, respectively. The pressure head required to maintain flow was so high that pulmonary edema occurred. The other three (N. L., M. G., and R. W.) had no evidence of pulmonary edema and had flow rates of 84, 90, and 95 c.c. per diastolic second. The pressures needed to maintain these flow rates, which were only 15 to 25 c.c. per diastolic second less than in the other two patients, were below the transudation level.

TABLE II. PHYSIOLOGIC DATA ON PATIENTS WITH MITRAL STENOSIS BEFORE AND DURING EXERCISE

PATIENT	STATE	MITRAL VALVE AREA ($CM.^2$)	PULMONARY EDEMA	PULMONARY "CAPILLARY" PRESSURE (MM. Hg)	MITRAL VALVE FLOW (C.C. PER DIASTOLIC SECOND)	DIASTOLIC FILLING PERIOD (SECONDS PER BEAT)	PULSE RATE	DIASTOLIC FILLING PERIOD (SECONDS PER MINUTE)	CARDIAC OUTPUT (LITERS PER MINUTE)	RESISTANCES (DYNES SECONDS $CM.^{-5}$)	
										PULMONARY ARTERIOLAR	TOTAL PULMONARY
J. D.	Rest	2.5	0	19	303	0.31	100	31	9.4	51	212
	Exercise		0	41	411	0.22	120	27	11.1	43	
J. F.	Rest	1.6	0	21	192	0.47	72	34	6.5	135	394
	Exercise		0	46	330	0.25	110	28	9.4	102	
L. T.	Rest	0.9	0	24	122	0.52	70	36	4.4	382	820
	Exercise		0	46	178	0.30	108	32	5.7	504	
M. B.	Rest	0.8	0	17	84	0.40	96	38	3.2	150	574
	Exercise		0	28	126	0.41	93	38	4.8	133	
E. S.	Rest	0.7	0	26	98	0.50	80	40	3.9	451	984
	Exercise		+	51	145	0.30	94	28	4.1	332	
	Rest	0.7	0	28	89	0.44	84	37	3.3	242	921
	Exercise		+	35	124	0.48	70	33	4.1	332	
N. L.	Rest	0.6	0	28	84	0.36	105	38	3.2	950	1650
	Exercise		+	35	120	0.24	136	33	4.0	960	
R. W.	Rest	0.6	0	34	95	0.49	75	37	3.5	274	1050
	Exercise		+	47			120		4.0	360	
M. M.	Rest	0.4	0	22	54	0.77	56	43	2.3	1150	1915
	Exercise*		0	35	82	0.25	136	34	2.8	1260	

*Exercise was performed for only a one-minute period instead of the standard three-minute period.

OBSERVATIONS DURING EXERCISE

Eight of the fifteen patients who were not in pulmonary edema at rest were exercised a total of nine times. The data are presented in Table II, and further details of the circulatory dynamics of these same patients will be found in Table I of a preceding report.[3]

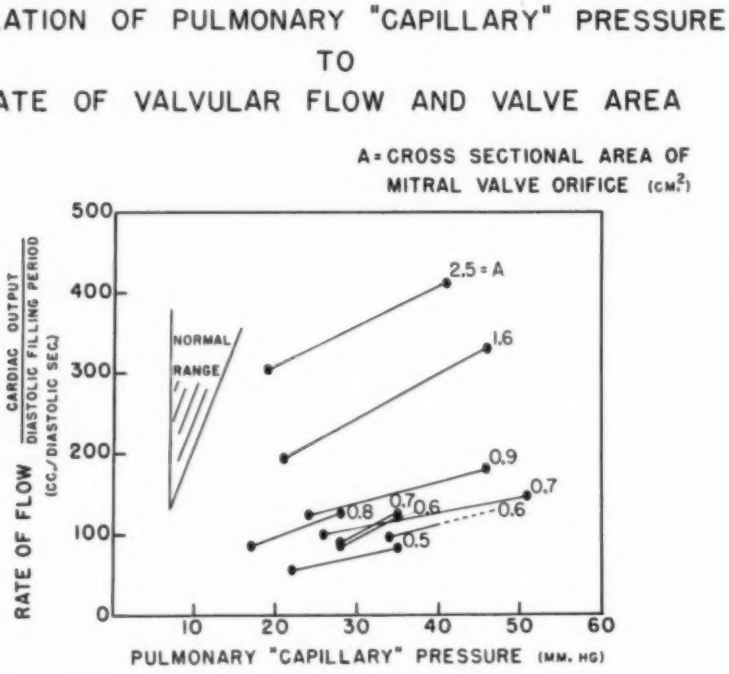

Fig. 3.—Pulmonary "capillary" pressure is plotted against mitral valve flow. It is seen that pulmonary "capillary" pressure rose on exercise in order to increase the valvular flow rate and that the greater the valvular stenosis, the more pressure was needed to do so.

I. Pulmonary Edema and Pulmonary "Capillary" Pressure.—Pulmonary "capillary" pressure rose on exercise in each patient (Fig. 3) and exceeded 35 mm. Hg in eight of the nine studies, although in only four of these eight studies (E. S. two times, R. W., and N. L.) did pulmonary edema develop. The failure of pulmonary edema to occur in the other four patients was attributable mainly to the short duration (one to three minutes) of the elevation of pulmonary "capillary" pressure as discussed elsewhere.[3]

II. Mitral Valve Flow.—In each patient the rate of mitral valve flow increased approximately one and one-half times on exercise (Fig. 3). To maintain the increased rate of flow, the pressure head on the mitral valve orifice had to rise. Because the orifices were so small, so much pressure was required to increase the rate of blood flow that the plasma osmotic pressure was exceeded in the pulmonary capillary bed, and in some patients pulmonary edema resulted.

The rate of flow depends on the required cardiac output and on the duration of the diastolic filling period.

A. Cardiac output: Cardiac output rose in four patients (J. D., J. F., L. T., and M. B.) and remained essentially unchanged in the others (Fig. 4). None of these four patients developed pulmonary edema, and two (J. D. and J. F.) had mild to moderate degrees of mitral stenosis. The increase in blood flow on exercise demanded an increase in the rate of valvular flow.

B. Diastolic filling period: The diastolic filling period was decreased on exercise in eight of the nine studies (Fig. 4). This decrease in time available during each beat for blood to flow through the mitral valve demanded an increase in the rate of the flow of blood through the valve if the required cardiac output was to be delivered to the tissues. The decrease in diastolic filling period was due to (1) increased heart rate (tachycardia occurred in seven of the nine studies with a resultant decrease in the duration of diastole) (Fig. 4) and (2) increase in the duration of ventricular systole. An abnormal increase in the duration of systolic ejection occurred in patient E. S. (second study), although the heart rate actually decreased on exercise. The period of ventricular systole on exercise lasted for 0.38 instead of 0.32 second at the pulse rate of 70. As a result,

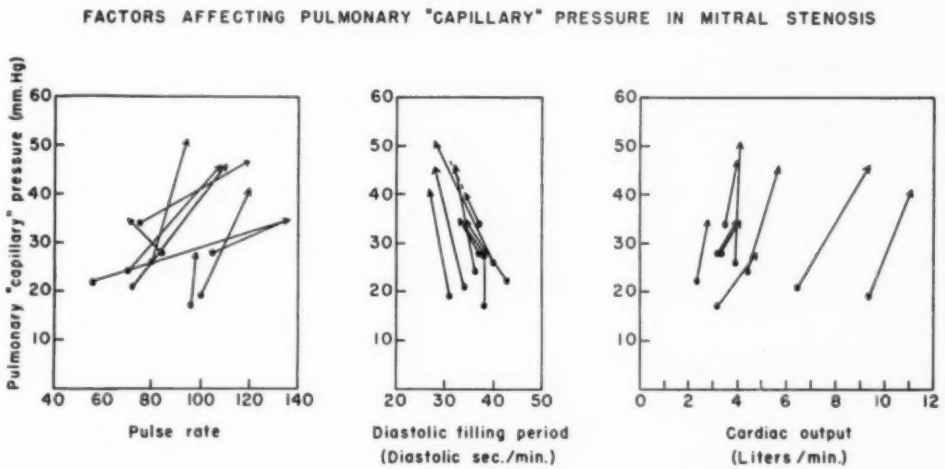

Fig. 4.—Pulmonary "capillary" pressure is plotted against (1) heart rate, (2) diastolic filling period, and (3) cardiac output. With exercise, in most patients, heart rate increased and diastolic filling period decreased; in some, cardiac output increased. In all, pulmonary "capillary" pressure increased on exercise. (See text for further discussion.)

the diastolic filling period per beat was 0.48 second instead of 0.54 second. With the slight increase in cardiac output and slight decrease in diastolic filling period that occurred here with exercise, pulmonary "capillary" pressure, in rising to increase the rate of flow through the valve, exceeded plasma osmotic pressure. Pulmonary edema ensued.

III. Mitral Valve Area.—The patients who developed pulmonary edema on exercise had severe degrees of mitral stenosis of the order of 0.6 to 0.7 $cm.^2$ Pressure levels rose steeply for only small increases in flow rate.

The effect of the degree of mitral orifice stenosis on the degree of pressure rise for a given flow is seen graphically in Fig. 3. In patient E. S., for example,

with a valve area of 0.7 cm.^{2}, pulmonary "capillary" pressure had to rise from 26 to 51 mm. Hg to increase the rate of flow of blood by 47 c.c. per diastolic second. This is shown mathematically:

$$98 \text{ c.c. per diastolic second} = 0.7 \text{ cm.}^2 \times 31\sqrt{26 - 5}$$
$$145 \text{ c.c. per diastolic second} = 0.7 \text{ cm.}^2 \times 31\sqrt{51 - 5}$$

A similar rise of pressure in J. D. from 19 to 41 mm. Hg increased the flow rate 108 c.c. per diastolic second. His valve area was 2.5 cm.^{2} Mathematically, this is shown as follows:

$$303 \text{ c.c. per diastolic second} = 2.5 \text{ cm.}^2 \times 31\sqrt{19 - 5}$$
$$411 \text{ c.c. per diastolic second} = 2.5 \text{ cm.}^2 \times 31\sqrt{41 - 5}$$

Any one of the factors increasing valve flow demanded an increase in pressure head in the lungs and left atrium. For example, on exercise cardiac output alone increased in M. B., pulse rate alone increased in M. M., and in E. S. the increase in duration of ventricular systole was in large part responsible for the increased flow rate.

DISCUSSION

I. Pulmonary Edema and Pulmonary "Capillary" Pressure

Pulmonary edema occurred at rest in all patients whose pulmonary "capillary" pressure rose to 35 mm. Hg or more and also in one-half the patients who exercised for one to three minutes. The occurrence of pulmonary edema at certain levels of hydrostatic pressure has also been seen in patients who had left ventricular failure from any cause.[22] No individual ever developed pulmonary edema in this laboratory without a marked elevation of pulmonary "capillary" pressure at the time. It is appreciated that the duration of elevation of pressure and a host of other factors will determine the amount of transudation and the severity of pulmonary symptoms.[3] No attempt has been made to relate 35 mm. Hg, as measured with respect to an arbitrary datum plane, to the individual hydrostatic-osmotic pressure balance.

II. Mitral Valve Flow

Factors Increasing the Rate of Flow.—Certain factors have been demonstrated both theoretically and experimentally to result in an increase in the rate of flow through the mitral valve. They were (A) increases in cardiac output and (B) decreases in diastolic filling period, due to increased (1) heart rate and (2) duration of ventricular systole. Conditions, such as exertion,[3,12] emotional upset,[13,14,15] thyrotoxicosis,[16,17] anemia,[18,19,20] fever,[21] pregnancy,[24,25] and possibly acute anoxia,[26] elevate cardiac output and/or pulse rate. In the presence of severe mitral stenosis, any one of them will lead to higher pressures in the pulmonary "capillary" bed and more frequent bouts of pulmonary edema. As discussed earlier, the increases in valvular flow could be accomplished only at the expense of more pressure energy. Accordingly, in order to deliver the required amount of blood to the body, left atrial and pulmonary "capillary" pressures rose. The possible mechanisms by which these pressures can be increased are discussed in a later section.

A. Cardiac output: The normal resting cardiac output in this laboratory ranges from 5 to 8 L. per minute, depending on body surface area.[21] At normal pulse rates, the average rate of flow through the mitral valve is between 150 and 300 c.c. per diastolic second (Fig. 2). Normal cardiac outputs and normal rates of flow were tolerated by patients J. D., J. F., L. B., and L. C. These patients had mild-to-moderate valvular stenosis.

In patients Gr. (both studies) and R. C., who had mitral stenosis of about 1 cm.^{2}, the cardiac output was normal. To maintain the necessary rates of flow of 175 and 156 c.c. per diastolic second, respectively, pulmonary "capillary" pressure had to rise above 32 mm. Hg. As a result, both patients developed symptoms of acute pulmonary edema. Thus, it is evident that in severe mitral stenosis a normal cardiac output cannot be maintained without literally drowning the patient. This is substantiated by the observations that blood flow as a rule is reduced in mitral stenosis[2,27,28,29] and that exercise, which may result in an increase in cardiac output, often precipitates pulmonary symptoms in mitral stenosis.[3]

B. Diastolic filling period: Decreases in this period result in increases in the rate of valvular flow. Such decreases are brought about by two factors:

1. Increased heart rate. As the heart rate increases, more time is occupied with ventricular systole and less time is left for diastole. In the normal heart, increases of pulse rate up to 180 to 200 have little effect on diastolic inflow because most filling occurs early in diastole,[11] but in mitral stenosis, where the entire period of diastole presumably is taken up with inflow, even small increases in pulse may exert great influence on the time available for inflow. Tachycardia can shorten the duration of diastole by five to twelve seconds per minute (Fig. 2). If the blood flow to the body is to be maintained despite the increased heart rate, the rate of valvular flow must rise. This can occur only if the pulmonary pressure head increases to the required level. This is why rapid heart action per se can lead to pulmonary edema in mitral stenosis.

The point is illustrated in patients D. K. and E. D. The cardiac output at pulse rates of 204 and 140, respectively, was maintained by the pressure elevation and the resulting increased flow rate through the valve. Paroxysmal tachycardia was frequently associated with paroxysmal pulmonary edema by history in our patients. The severity of the tachycardia determined the degree of increase in valve flow rate necessary to keep up the required blood flow to the tissues. Hence, one of the factors affecting the height of the pulmonary pressure head was the severity of the tachycardia. Variations of only 20 or 40 beats per minute could make the difference between the presence or absence of pulmonary edema.

When the tachycardia is severe enough, the diastolic filling period may be so reduced that pressure levels far beyond the pumping ability of the right ventricle may be required to maintain cardiac output. Under these conditions, blood flow falls off sharply. It is easy to see that with severe tachycardia a patient may be trapped between pulmonary edema and peripheral circulatory collapse.

2. Duration of ventricular systole. Just how frequently the duration of ventricular systole is prolonged abnormally is not known. When it does occur, there is less time available for diastolic filling per beat. This may be important in the presence of mitral stenosis. This increase occurred on exercise in patient E. S. for unknown reasons and illustrated how, although the heart rate decreased, there was actually less time available than previously for blood to flow through the mitral valve. Increases in resistance beyond the left ventricle, from aortic stenosis or systemic hypertension, might increase the period of systolic ejection and thus decrease the diastolic filling period. In mitral stenosis complicated by such disorders, pulmonary "capillary" pressure should rise if cardiac output is maintained at a given level. No data were available in this selected series on this point. Certainly, it would seem that greater elevations of pulmonary "capillary" pressure and a more frequent occurrence of pulmonary edema should be seen in association with diseases affecting the left ventricle even before gross failure of that ventricle occurs, because of the abnormal shortening of the time for diastolic inflow.

Factors Decreasing the Rate of Flow.—Under certain conditions the mitral valve flow rate may be reduced. These will now be taken up in order.

A. Cardiac output:

1. Effect of pulmonary arteriolar and total pulmonary resistance. Mentioned in earlier studies[2] was the frequent elevation of pulmonary arteriolar and total pulmonary resistance in the presence of severe mitral stenosis. Because of this, the right ventricle was greatly hampered in its ability to pump blood at the high pressures necessary to keep up blood flow. As a result, cardiac output tended to be low and quite stable in patients with high pulmonary resistances. It would seem logical, then, that these patients would be less prone to the paroxysmal attacks of pulmonary edema resulting from sudden surges of cardiac output and mitral valve flow, while those patients with low or moderate resistances and severe mitral stenosis frequently should develop acute pulmonary edema. This was borne out in the patients studied. Patients R. C. and Gr., with low pulmonary arteriolar resistances and severe valvular stenosis, had normal or elevated outputs at rest and were in pulmonary edema. Both had histories of recurrent acute pulmonary edema. In contrast, only two (McL. and D. V.) of the six patients with pulmonary arteriolar resistances greater than 600 were in pulmonary edema at the time of study; neither had a history of paroxysmal pulmonary edema nor were blood flows elevated at the time of study. Each had tachycardia and a shortened diastolic filling period. This was believed to have precipitated pulmonary edema.

Anatomic changes in the intrapulmonary arterioles described by Parker and Weiss[30] and Larrabee, Parker, and Edwards[31] support the physiologic evidence of vessel narrowing. Why the change is found to a variable degree in different patients exposed to the same pressure-flow effects and whether anatomic vessel change correlates with physiologic evidence of high resistance is unknown. That it serves a "protective" function in reducing and stabilizing cardiac output has been shown in this study.

2. Effect of right ventricular failure. When the right ventricle fails, either because of a high pressure load (No. 1 above) or a faulty myocardium, as in acute rheumatic carditis, cardiac output becomes reduced. As considered earlier, the mitral valve flow rate will be less. It is a common experience to observe the relief of severe pulmonary congestive symptoms with the onset of right ventricular failure.

3. Effect of hypothyroidism. Patients with hypothyroidism have a low cardiac output.[32] Their valvular flow rates become decreased. Hence, one can understand readily the beneficial effects of thyroid ablation on pulmonary symptoms in mitral stenosis.

B. Diastolic filling period: When the heart rate is kept at normal or decreased levels by rigid control of fibrillation, as can usually be achieved with digitalis, the mitral valve flow rate will be decreased because of the extra time available for diastolic inflow.

In all of these states in which blood flow through the mitral valve is decreased, pulmonary "capillary" pressure may approach normal levels, even though the mitral stenosis is severe, because the bodily demands for blood flow are low.

III. Mitral Valve Area

The amount of elevation of pressure for a given flow varies inversely as the square of the valve orifice area. This is seen in Fig. 5. As the area decreases, the pressure required to maintain a given flow becomes inordinately large. For example, patients L. B., Gr. at rest, and L. T. during exercise, had similar valve flows. Yet, because mitral valve areas were 1.4, 1.1, and 0.9 cm.^{2}, respectively, the pulmonary "capillary" pressures had to be 20, 38, and 46 mm. Hg, respectively. It is remarkable that, with the usual bodily demands for blood flow at rest, in patients with valve areas of 1.0 cm.^{2} or less, pressures in the lung do not rise above the transudation level more often than is observed.

The exponential relationship of flow and area to pulmonary pressure may serve to explain some clinically and experimentally observed phenomena. For example, the sudden onset of pulmonary symptoms that occurs as the mitral valve gradually becomes narrower may be explained by the sudden large increases in pressure head in the pulmonary circuit required to maintain blood flow. In similar fashion, the disproportionate rises in pulmonary artery pressures in relation to cardiac output on exercise in mitral stenosis, noted by Hickam and Cargill,[12] rather than being due to increased pulmonary arteriolar resistance may have reflected the pronounced rises in pulmonary venous and pulmonary "capillary" pressures demanded by higher flows through the stenotic mitral valves.

IV. Effect of Left Ventricular Diastolic Pressure on Pulmonary "Capillary" Pressure

The last factor which may change pulmonary "capillary" pressure in the original equation is left ventricular diastolic pressure. No observations have been made of this pressure in patients with mitral stenosis. According to the equation, however, pulmonary "capillary" pressure will rise in additive fashion

as left ventricular diastolic pressure rises. Thus, whereas exponential changes in pressure values occur as flow and area change, the characteristic curve of pulmonary "capillary" pressure and flow (Fig. 5) is shifted to the right by failure or strain of the left ventricle. In the selected group of patients presented here, only one (N. L.) had clinical evidence of active rheumatic fever. It was believed

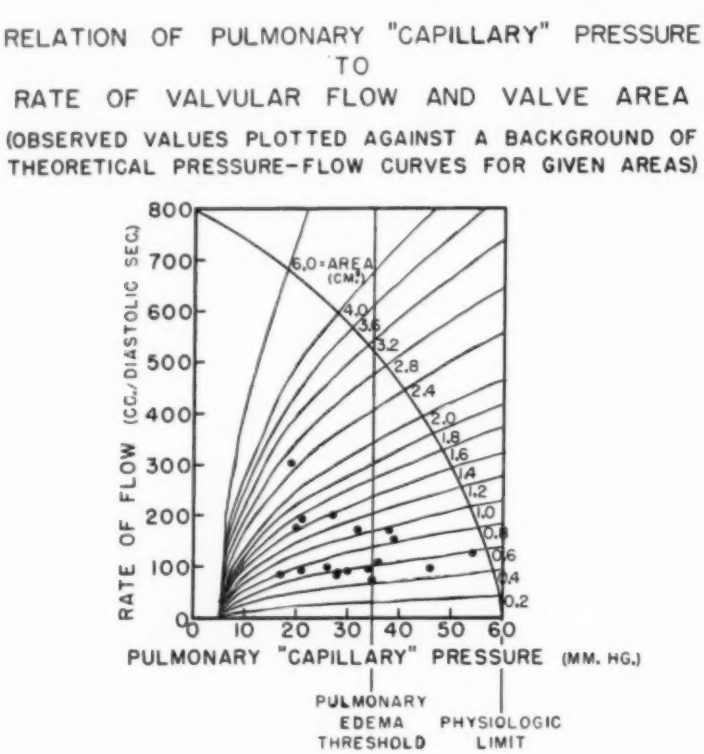

Fig. 5.—In this figure are seen theoretical curves of pulmonary "capillary" pressure and mitral valve flow as they obtain at different mitral valve areas. It will be observed that as mitral valve area decreases, more and more pressure is required to maintain a given rate of flow. At some point a given blood flow can be maintained only if pressure exceeds 35 mm. Hg: then symptoms of pulmonary edema occur.

that few of the patients had an active diffuse myocarditis such as might result in significant elevations of left ventricular diastolic pressure. Because the left ventricular work, both pressure and kinetic, does not change essentially with exercise in severe mitral stenosis,[3] the left ventricular diastolic pressure probably changed little from the resting to the exercising state in our patients. Therefore, the rises in pulmonary "capillary" pressure could properly be attributed mainly to kinetic energy losses through an orifice.

The Method by Which Pulmonary "Capillary" Pressure is Elevated

Previous discussion has been concerned with the factors which may require an elevation in pulmonary "capillary" pressure head. How is this pressure increased in order to maintain blood flow?

Pulmonary Venous-Left Atrial Volume-Elasticity Characteristics.—The level of pressure in the pulmonary venous-left atrial compartment depends upon the volume-elasticity properties of this compartment. Pressure will rise only if (1) more blood is added to the compartment or (2) the volume-elasticity properties change so that the same blood volume exerts a greater pressure.

1. Increase in blood volume: The relation between volume and pressure is not linear within the pulmonary venous-left atrial chamber. The two are related along a curve, as shown in Fig. 6, which may vary somewhat from patient to patient,[33] although its general shape is characteristic of venous-tissue. Curves similar in shape have been reported by Little[34] for the left atrium. At low pressures, the volume required to change the pressure is great, while at high pressures the volume changes required are small.

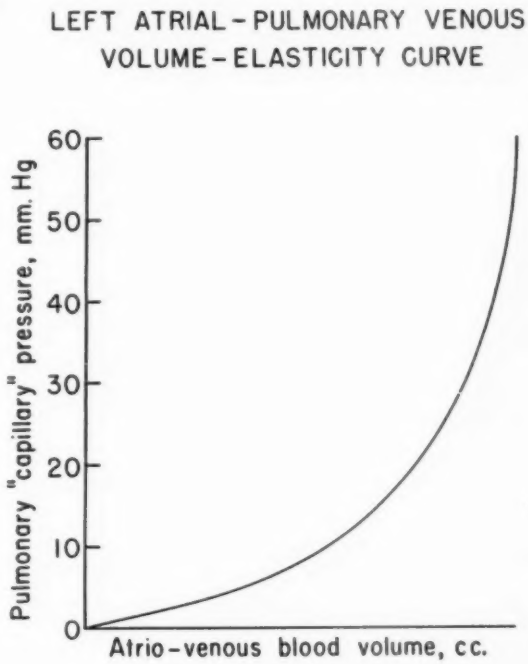

Fig. 6.—Theoretical pressure-volume curve of pulmonary veins and left atrium. Pulmonary "capillary" pressure, an index of pressure in the pulmonary venous-left atrial compartment, is plotted against pulmonary blood volume. Pressure and volume are related along a curve of changing slope.

2. Change in elasticity properties:

(a) Pulmonary veins. Whether or not pulmonary venous constriction occurs with alteration of its elasticity properties in mitral stenosis is as yet unsettled. Studies in this laboratory[10] have failed to demonstrate a measurable gradient between pulmonary "capillary" and left atrium over a wide range of physiologic conditions, suggesting that (1) no venous constriction occurs, (2) both left atrium and pulmonary veins constrict as one chamber, or (3) pulmonary venous constriction is not so great with respect to the venous cross-sectional

area in relation to flow as to cause measurable kinetic energy losses between the two parts of the chamber. Therefore, it is believed that pulmonary "capillary" pressures accurately reflect changes in left atrial pressure.

(b) Left atrium. Although no acute changes in physical volume-elasticity properties of the atria have been reported experimentally as yet other than during the period of atrial systole,[35] this type change cannot be ruled out as the cause of acute pressure elevation to meet increases in flow. Variations in the size of left atria in patients with mitral stenosis would suggest that there is some effect of the underlying rheumatic disease on atrial pressure-volume characteristics and that the properties may gradually change over the course of years, but whether acute variations occur is not known.

In the absence of decisive evidence concerning venous or atrial constriction, we are inclined to believe that the pressure rises because pulmonary and atrial blood volume has been increased. This can be accomplished only by a momentary imbalance in ventricular outputs. For example, if blood flow is maintained at 4 L. per minute but the pulse is suddenly doubled and the diastolic filling period decreased, the right ventricle will continue to discharge 4 L. per minute, while the left ventricle momentarily will discharge less than 4 L. per minute. This occurs because at the pre-existing pulmonary pressure less blood is pushed through the valve in the shortened filling period. The discharge of the right ventricle momentarily increases pulmonary and atrial blood volume, the pressure head rises, and finally the flow rate through the mitral valve is increased. The left ventricle again discharges 4 L. per minute.

The volume-pressure relations in a particular vascular bed depend on the elasticity properties of the vasculature involved. The more rigid the vessels the less is the increase in blood volume needed to increase the pressure within the vessels. This is illustrated by the fact that 10 c.c. of liquid within a segment of artery may exert a pressure of 50 mm. Hg, while 10 c.c. within a vein of equal length may exert a pressure of only 10 mm. Hg. If the pulmonary veins and left atrium are more rigid than normal, then the amount of blood required to increase pressure to a certain height will be less, and, if the vessels are less rigid, then more blood will be required. That great variations in veno-atrial blood volume probably do occur from patient to patient is attested to by x-ray and autopsy observations of the size of the left atrium. In our experience, individuals with similar pulmonary "capillary" pressures do not all have atria of the same size.

In those patients with small, thick-walled atria, due to the particular shape of their pressure-volume curve, at the high pressures seen in mitral stenosis where the vascular compartments are already filled to their elastic limit, probably very small increases in pulmonary and left atrial blood volume are necessary to elevate the pressure head to the required level. The volume increase is small yet the pressures rise steeply. The tolerance as regards pressure for volume change in these patients is extremely low, and acute pulmonary edema can readily occur. On the other hand, there are some patients who have paper-thin atria which may contain as much as a liter or more of blood at low pressures. This type of atrium may be thought of as an hydraulic surge or shock chamber; large volumes of blood may be accommodated without much of a rise in pressure.

Thus, elevations in atrial pressure cannot occur suddenly, and paroxysmal pulmonary edema should be less common in these patients than in those with small "tight" atria.

Borden and associates[6] reported that the blood volume in the pulmonary, left heart, and large artery compartment of the circulation was normal in patients with mitral stenosis. There are several interpretations of this observation: (1) The technique utilized is a measure of the volume of blood in the pulmonary capillaries and veins, left auricle and ventricle, and large arteries. In individuals with a normal circulatory system, the curve of dye concentration appearing in the femoral artery after its injection into the pulmonary artery can easily be extrapolated to give interpretable readings, while in the presence of left ventricular failure or mitral stenosis, the slowness of the circulation may alter the dye curve in such fashion as to introduce a large error in extrapolation and, therefore, of estimation of blood volume. (2) It is possible that an increased blood volume in the pulmonary capillary, pulmonary venous, and left atrial compartment would be masked by a decrease in the blood volume in the left ventricle and large arteries in mitral stenosis. (3) Either the degree of mitral stenosis or the rate of valvular flow may have been so low in their patients that the required atrial pressure level was not high, and therefore the increase in blood volume over the normal was not large enough to be detected by the methods used. (4) The elasticity modulus of the vascular bed in these patients may have been such that a given volume of blood exerted a greater pressure in their vessels than in the vessels of a normal person, i.e., the vasculature was more rigid than normal. Thus, while the vessels could be distended close to capacity, the capacity might actually have been less than the normal. Pulmonary blood volume must always be considered in relation to vascular bed capacity or "elasticity." The problem may be likened to that of oxygen in the blood. The relation of blood "content" to vascular "capacity" gives the elasticity "saturation," and this saturation maintains the observed pressure.

The Role of the Right Ventricle in Increasing Pulmonary Pressures.—The ability of the right ventricle to pump blood at the required pressures is a major factor in altering mitral valve flow. When the ventricle readily delivers more blood at higher pressures into the lungs, valvular flows are readily increased. Blood flow is maintained, but the lungs are congested. When the right ventricle can no longer deliver the required pressure to move the blood, sudden surges in valve flow no longer are possible. With the onset of right ventricular failure, paroxysms of pulmonary edema often cease.

CONCLUSION

It became clear from this study that the occurrence of pulmonary edema did not depend on the degree of mitral stenosis directly, but rather on the required rate of blood flow through the valve at the moment. Increases in valve flow rate have been shown to be the *raison d'être* for the elevations of pulmonary "capillary" pressure. Therefore, although the degree of stenosis becomes a leading factor in the regulation of pulmonary pressure by fixing the particular

curve of relationship of pressure and flow, the rate of required valvular flow actually fixes at what point on the curve a given patient is at a given time. If the required hydrostatic pressure exceeds the plasma colloid osmotic pressure, transudation will occur and symptoms will appear if pressure is maintained long enough. Thus, in a patient with severe mitral stenosis, variations in the heart rate and the cardiac output by leading to increases in valvular flow rate become the major determinants of pulmonary edema.

SUMMARY

1. Pulmonary edema occurred at rest in six patients and during exercise in three other patients with severe mitral stenosis during cardiac catheterization.

2. Pulmonary "capillary" pressure was 32 mm. Hg or higher in all nine patients.

3. Pulmonary "capillary" pressure, actually an index of left atrial pressure, was elevated to such high levels in order to maintain blood flow through the mitral valve.

4. Factors which resulted in an increased mitral valve flow rate, thus requiring an elevation in pulmonary "capillary" pressure, were (a) increased cardiac output and (b) decreased diastolic filling period. The latter was decreased by increases in (1) heart rate and (2) duration of ventricular systole.

5. The degree of anatomic mitral stenosis affected the degree of pulmonary "capillary" pressure rise in exponential fashion.

6. The mechanism of elevation of pulmonary "capillary" pressure was believed to be a momentary imbalance in ventricular outputs such that pulmonary blood volume and pressure were increased.

7. It has been demonstrated that in patients with mitral stenosis, a normal cardiac output can be delivered only at the expense of high pulmonary "capillary" pressure.

8. The role of tachycardia, even of a mild degree, in producing or aggravating symptoms of pulmonary edema is emphasized.

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HEART PUNCTURE

II. Cardioangiography: Clinical and Electrocardiographic Results

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IN A preceding paper[1] we have referred to the physiological and experimental aspects of heart puncture. In the present article we shall make reference to the heart puncture as a method of visualizing directly the ventricular chambers of the heart as well as the great vessels by means of a radiopaque substance.

We have called this procedure "cardioangiography" in order to distinguish it from the classical angiography introduced by Castellanos and associates[2] and Robb and Steinberg,[3] because instead of introducing the Diodrast into a peripheral vessel, we inject it directly into the heart. Employing this technique, we inject 50 c.c. of 75 per cent Diodrast under a pressure of 25 pounds into the right ventricle and of 30 pounds into the left. We will not describe the technique further because it has been presented in detail in the preceding paper.

Following this procedure, we studied thirty patients in whom we have practiced forty-five punctures without fatal accident.

Age:

Average age	60 years
Highest age	92 years
Lowest age	24 years
A group between 50 and 80 years	15 cases

Clinical Diagnosis:

Lung carcinoma	10
Tuberculosis of the lung	3
Aortic regurgitation	3
Asthma	2
Bronchiectasis	2
Mediastinal syndrome	2
Essential hypertension	2
Lung abscess	1
Cor pulmonale chronic	1
Syphilitic aortitis	1
Aortic aneurysm	1
Chronic coronary disease	1
Pseudobulbar paresis	1

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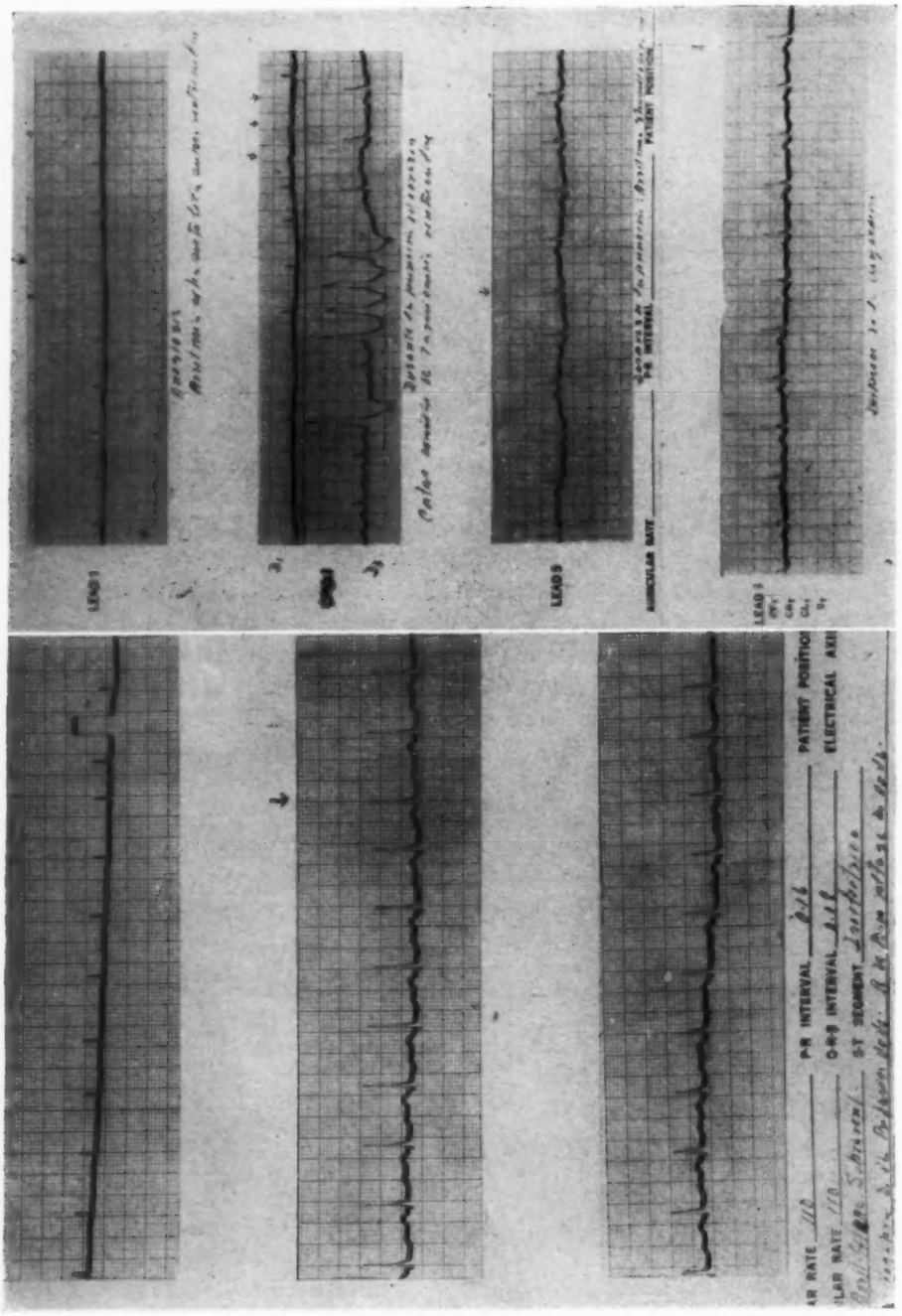

A.

B.

Fig. 1.—*A*, Electrocardiogram showing some auricular extrasystoles before the cardiac puncture. One of them is indicated by the arrow. *B*, Electrocardiograms of the same patient taken during and after the cardiac puncture. Leads I and III show some ventricular extra systoles that disappeared spontaneously in Lead III.

Patients' General Condition:

Satisfactory	3
Fair	10
Bad	11
Very bad	6

Number of Punctures Made on Each Patient:

19 patients	1
7 patients	2
4 patients	3

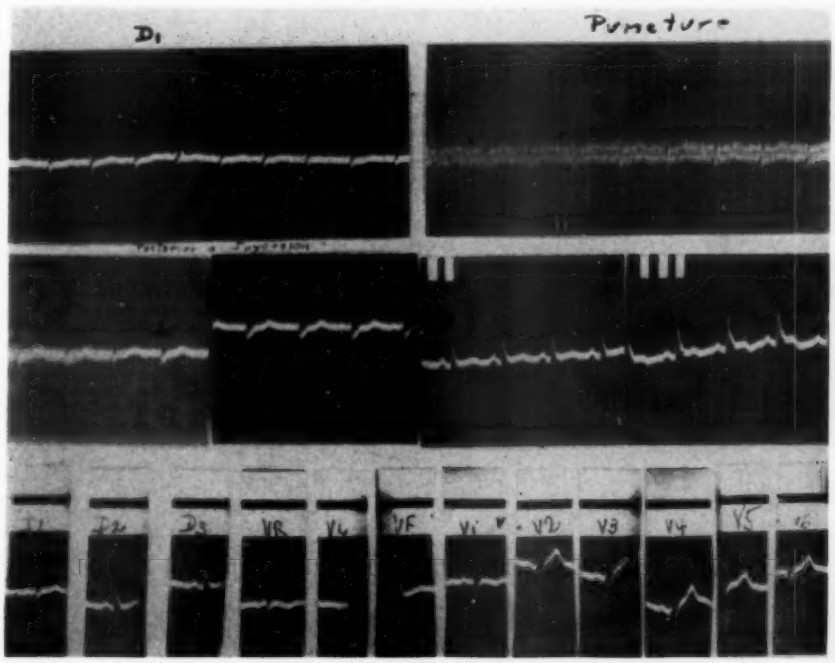

Fig. 2.—Electrocardiogram before and during the cardiac puncture. The fibrillated aspects of the record correspond to the permanence of the trocar in the right ventricle. Immediately after the introduction of the radiopaque substance, a right bundle branch block was registered as is shown by the arrow. In the lower part of the photograph there is an electrocardiogram taken a few hours after the procedure that shows the absence of the bundle branch block.

The large number of punctures practiced on several patients was determined by the desire to study the right and left chambers in different positions. The time between two punctures was forty-eight hours, although in two cases they were practiced one immediately after the other. The right ventricle was punctured on thirty occasions, while the left one was punctured only fifteen times.

The reason for the high incidence of the puncture into the right ventricle was that a higher percentage of the patients presented some type of pulmonary disease, and we were interested in the vascular alterations of the pulmonary vessels.

In only two cases did we fail to obtain the desired result. The probable explanation of this failure is surely related to a marked heart deviation due to the pulmonary disease present in these two cases.

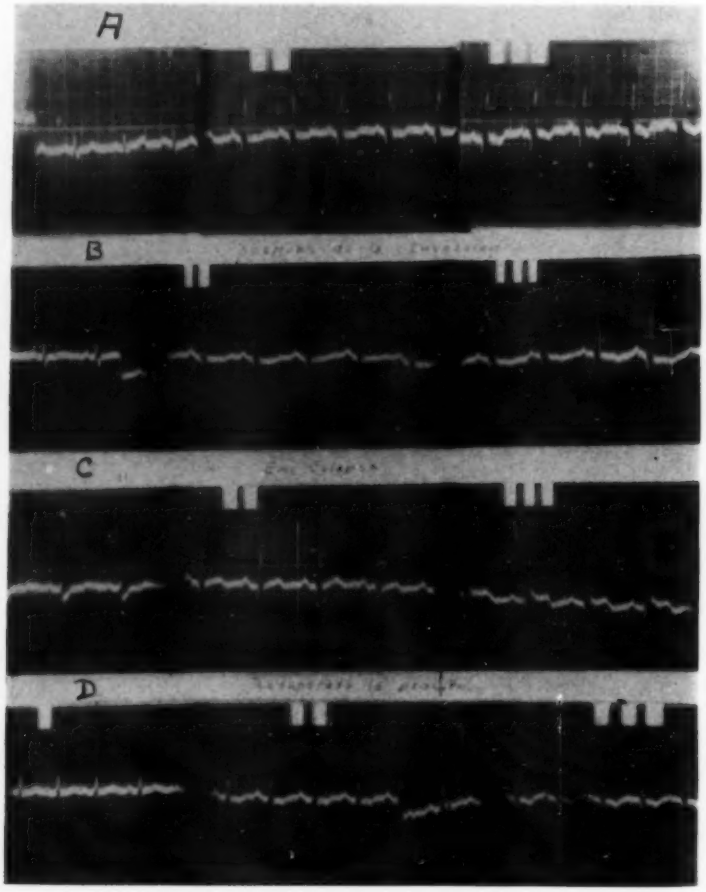

Fig. 3.—*A*, Electrocardiogram taken before the puncture from a 60-year-old patient with an aortic regurgitation. *B*, Changes of the T wave in Lead III occurring at the last moment of Diodrast injection. *C*, Transient right bundle branch block that appeared only a few seconds after the Diodrast injection. This coincided with a fall of the blood pressure to zero. The positive displacement of the ST segment in Lead III was also observed during the extreme hypotension. *D*, Electrocardiogram showing the disappearance of all the changes when the blood pressure returned to previous levels after an injection of Coramine-ephedrine.

The recognition of the ventricular chambers into which the trocar was introduced is easily established by the color and the characteristic way in which the blood comes out from each ventricle.[1]

OBSERVATIONS

Symptoms After the Puncture.—Eighteen patients did not present any subjective symptomatology after the slight anesthesia. A proof of this lack of subjective symptoms is that several patients agreed to be punctured without any

objection. Eight patients complained of a slight disturbance either in the upper abdomen or at the retrosternal region. These troubles were so slight that they did not require any analgesia and disappeared spontaneously within twenty-four hours.

It is worth while to note that two patients with lung carcinoma reported some amelioration after the procedure which was interpreted, of course, as a psychological reaction. We observed this improvement in two other patients, in whom dyspnea and cough disappeared.

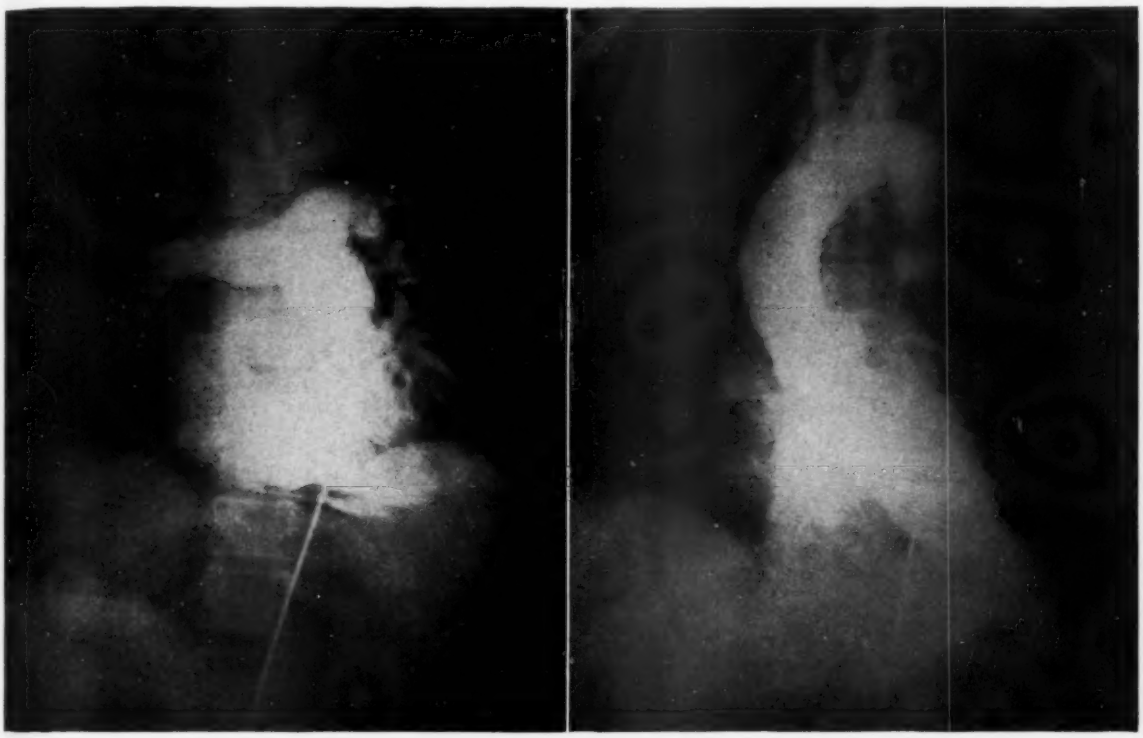

Fig. 4. Fig. 5.

Fig. 4.—Normal view of the right ventricle with the pulmonary artery and its branches.

Fig. 5.—Normal view of the left ventricle with visualization of the papillary muscles, aortic arch, and descending aorta.

Study of the Pulse.—During the injection of the Diodrast there was a discrete tachycardia in several cases, the pulse returning to normal frequency rapidly. The subsequent study of the pulse revealed no abnormalities in any case.

Study of the Blood Pressure.—We did not notice any variations of the blood pressure during the puncture. On the other hand, during the injection of the Diodrast the blood pressure descended 10 to 40 mm. Hg systolic in most cases. In one patient the pressure went down to 0, but it rapidly returned to normal

after the administration of Coramine-ephedrine. The day after the puncture almost all the patients presented their usual blood pressure level.

Auscultation.—None of the patients presented any auscultatory abnormality of the heart on the days following the puncture.

Fluoroscopic Examination.—Twenty-seven of the thirty patients were examined by fluoroscopy on the following days, and none presented any changes in heart or lungs.

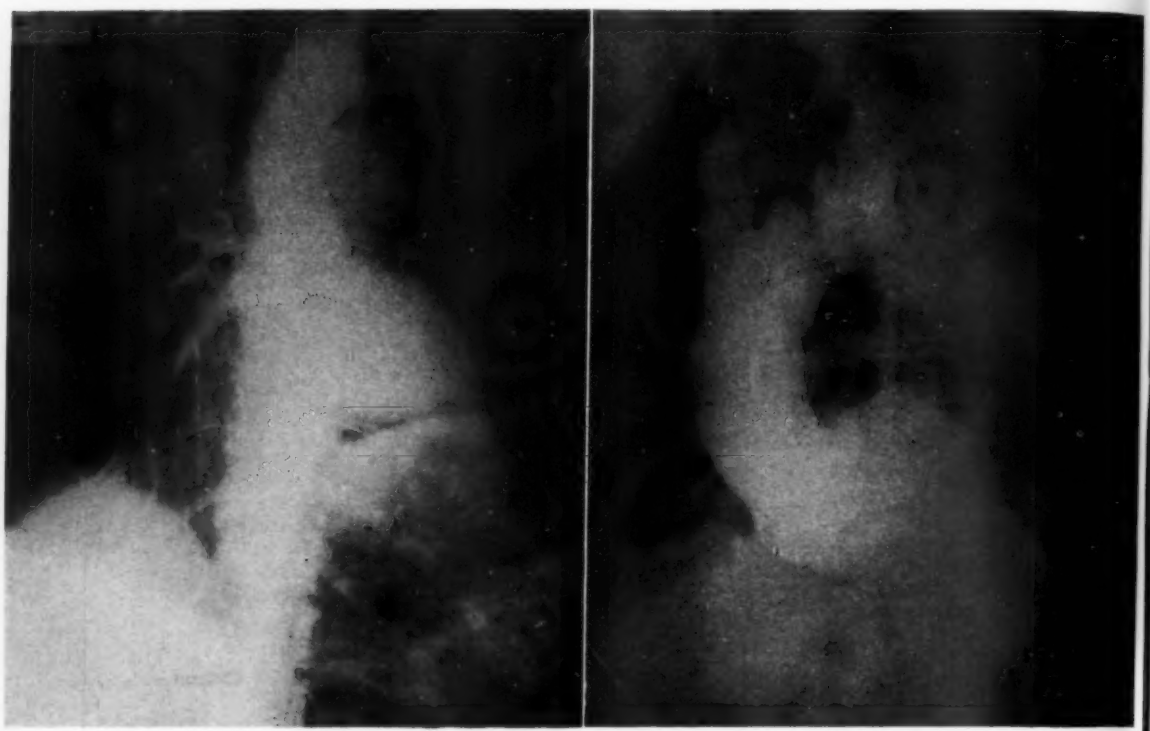

Fig. 6. Fig. 7.

Fig. 6.—Visualization of the pulmonary veins in a patient with mitral insufficiency by injection of Diodrast into the left ventricle.

Fig. 7.—An aneurysm of the thoracic aorta visualized by injection into the left ventricle.

Temperature.—In only three cases was there a moderate temperature rise the day after the puncture. The interpretation of this was very doubtful because the patients had bronchial carcinomas and had previously had fever. The three patients with pulmonary tuberculosis did not present any variation in their fever.

Electrocardiographic Findings.—All the patients were checked with an electrocardiogram before, during, and after the puncture and injection of Diodrast, as well as on the following days.

The electrocardiographic changes were of minimal importance. The most frequent alteration found was that due to ventricular extrasystoles, especially at the moment the trocar penetrated the ventricular wall, disappearing in almost every case once the trocar reached the chamber (Figs. 1 and 2).

The case that presented more important electrocardiographic changes was the one in which the blood pressure fell to zero as a result of the Diodrast injection, as may be seen in Fig. 3. The interpretation of these changes was related to the fall of the blood pressure because they disappeared immediately after the blood pressure reached its normal level.

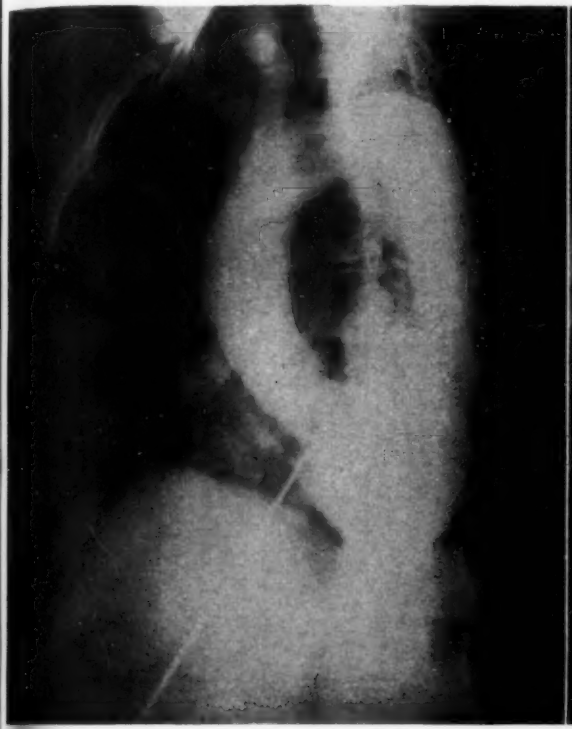

Fig. 8.

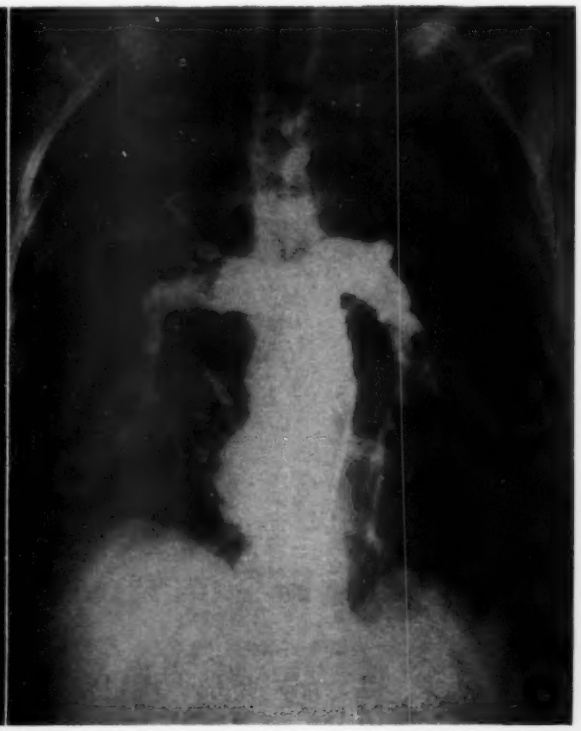

Fig. 9.

Fig. 8.—Visualization of a dilated aorta and its branches in a syphilitic patient. The trocar can be seen entering the left ventricle.

Fig. 9.—A patient with lung carcinoma who was punctured in the right ventricle. Alterations of the pulmonary artery branches can be seen.

The other most important electrocardiographic alteration was a transient right bundle branch block of very short duration which was observed on four occasions immediately after the Diodrast injection into the right ventricle. We believe that the appearance of this block was due to the rapid rise of pressure within the ventricle produced by the fast injection of 50 c.c. of the opaque substance. None of the patients, except the above-mentioned, presented any abnormalities of the T waves or the ST segments indicative of ischemia or actual lesion.

One patient with a lung carcinoma who showed electrocardiographic signs suggestive of a posterior wall infarction, confirmed at autopsy, did not present any variation of the record either during or after the cardioangiography.

RESULTS

Opacification of the ventricular chambers and great vessels was obtained with perfect clearness (Figs. 4, 5, 6, 7, 8, 9, 10, and 11). The x-ray films of the left ventricle and the aorta had a density and precision more accurate than those obtained by the angiocardiographic method. Most of the patients in whom this ventricle was injected permitted magnificent visualization of the coronary arteries.

In two cases suggestive of mitral insufficiency the diagnosis was confirmed when the opaque substance introduced through the left ventricle appeared in the pulmonary veins, having passed through the mitral orifice. None of the patients without this valvular defect showed this retrograde opacification.

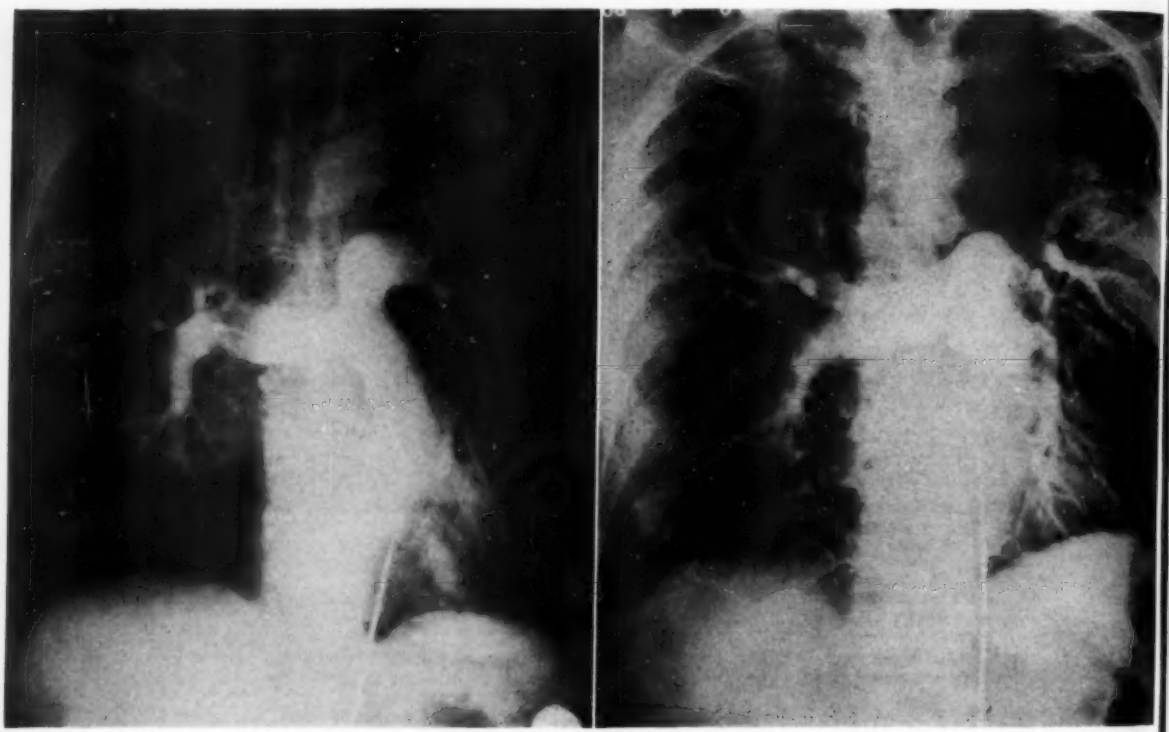

Fig. 10. Fig. 11.

Figs. 10 and 11.—Two patients with lung carcinoma who were punctured in the right ventricle Alterations of the pulmonary artery branches can be seen.

All the patients with lung carcinoma demonstrated a sudden arrest of the Diodrast within the pulmonary vessels in the affected area as well as compression of the pulmonary artery.

In patients with moderate aortic disease it was possible to outline the course of the blood flow from the left ventricular chamber to the abdominal aorta and its branches. We regret we could not use a seriograph in order to obtain several x-ray films and thus make a much more complete study of the cases.

There was no opportunity to employ the method in patients with coarctation of the aorta and auricular septal defect, but we believe that it would give x-ray films capable of establishing the correct diagnosis in such cases.

PATHOLOGICAL STUDY

When this paper was completed, there were five deaths of the patients whose cases were reported. They died seven and twenty-eight days, two, three, and four months, respectively, after the heart puncture. All the patients died because of lung carcinoma and metastases. The last four did not show evidence of the puncture in the pericardium, myocardium, or endocardium, although the last two were punctured on three occasions. The first patient died seven days after the puncture and presented a lung carcinoma with metastases to brain, liver, and adrenals. There were also small blood clots in the pericardial sac in a reabsorbing stage.

SUMMARY

We have studied the radiological, electrocardiographic, and clinical aspects of heart puncture in man.

This method was employed forty-five times in thirty different patients without mortality or serious harm.

We think that heart puncture in man can be utilized for diagnosis; undoubtedly, it should be of great value in the study of the physiology and pathology of the cardiovascular system.

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THE SPREAD OF THE EXCITATORY PROCESS AND THE LEFT VENTRICULAR CAVITY POTENTIALS IN LEFT BUNDLE BRANCH BLOCK AS STUDIED WITH ESOPHAGEAL LEADS

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NEW YORK, N. Y.

THE spread of the electrical excitatory process in the ventricles during normal conduction has been studied by electrocardiograms recorded directly from the heart in animals[1,2] and in man,[3] but less complete information is available on the spread of the excitatory process, especially in the posterobasal surface of the heart, in the presence of left bundle branch block. In left bundle branch block, delayed activation of the left ventricle has been demonstrated with resultant delay in the contraction of the left ventricle as compared to the right.[4-9] In experimentally produced left bundle branch block in animals[10,11] and in cases of left bundle branch block in man,[12] the left ventricular cavity potentials recorded directly from inside the left ventricle have been shown to be initially positive, instead of initially negative as noted in the presence of normal conduction.[13,14] It has been shown that the potential variations recorded at the epicardial surface of a transmural infarct are usually similar to those of the adjacent parts of the ventricular cavity.[15,16] Hence, a familiarity with the left ventricular cavity potentials in cases of left bundle branch block may be of some value in interpreting the left precordial leads in the presence of a transmural infarct in patients with such a conduction defect and in distinguishing left bundle branch block from left ventricular hypertrophy.

Esophageal electrocardiography has made it possible to study the potentials of the human left ventricular cavity without resorting to the more complex procedure of left heart catheterization. Esophageal electrocardiograms taken at a certain level of the left atrium, in the presence of an atrial intrinsic deflection, have been shown to reflect essentially left ventricular cavity potentials, and leads taken below this level record the potentials of the posterior and diaphragmatic surface of the heart.[17,18] The proximity of the esophageal electrodes to the diaphragmatic and posterior surface of the heart affords a readily available method for recording the potentials of the posterior aspects of the heart[18] and for timing the intrinsicoid ventricular deflections. In addition, the use of esophageal leads in studying the RS-T segment displacement inside the left ventricle has avoided

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the possible RS-T segment deviations caused by the contact of the tip of an intracardiac electrode with the endocardium.[19,20]

In this study, the simultaneous recording of esophageal and unipolar precordial leads was utilized to study the spread of the excitatory process in the ventricles and the potentials of the left ventricular cavity in persons with left bundle branch block.

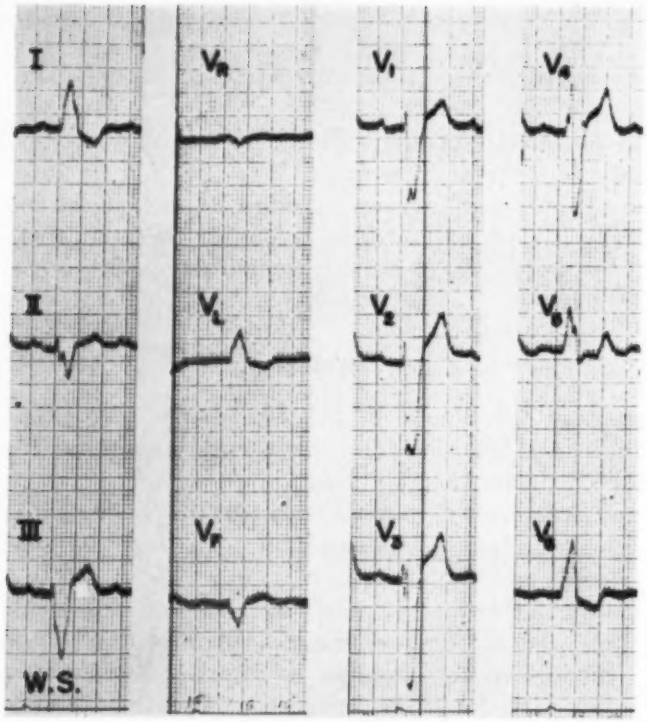
METHODS

Fifteen cases of left bundle branch block were selected according to the criteria of Wilson and associates.[21] The electrocardiograms revealed a broad notched or bifid QRS complex of 0.12 second duration or longer, and there was a delay in the appearance of the intrinsicoid deflection in the left precordial leads. Varying degrees of cardiac enlargement due to hypertensive or arteriosclerotic heart disease were present.

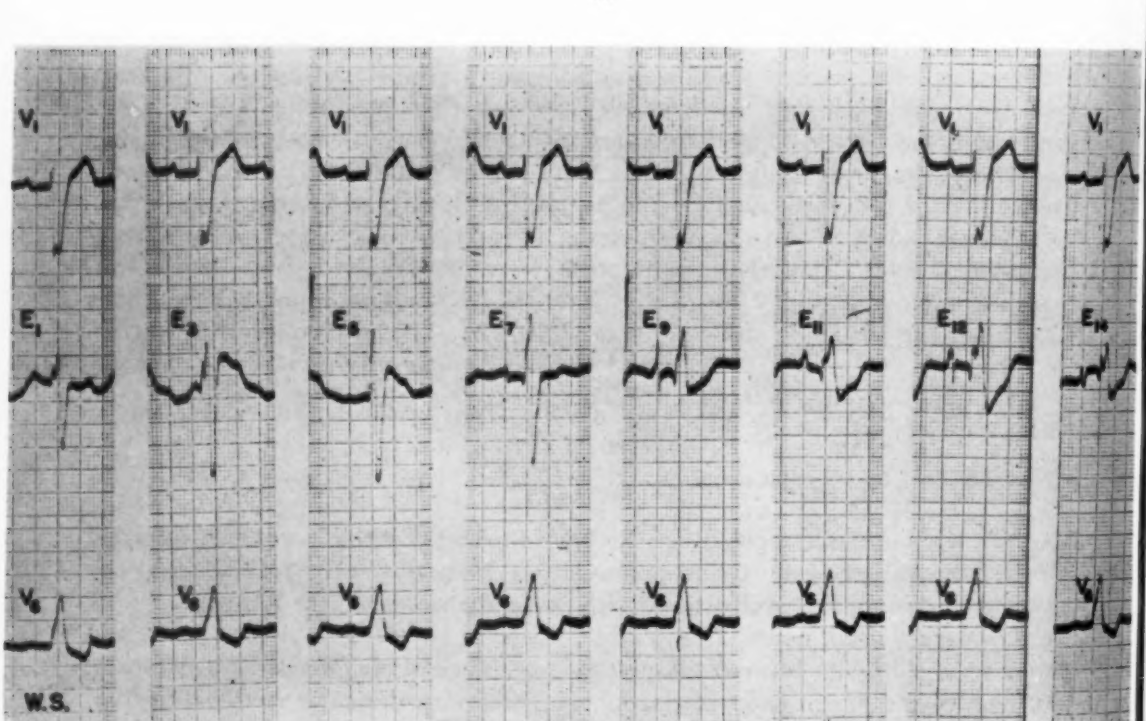
The methods employed in this study were similar to those already described in more detail elsewhere.[19] An esophageal lead consisting of a fine rubber tube containing a central core of fifteen fine wires, each separately connected to external metal bands placed 1.75 cm. apart, was passed under fluoroscopic control to below the level of the diaphragm into the fundus of the stomach. This electrode permitted the recording of a regular sequence of fifteen esophageal electrocardiograms from the posterior and diaphragmatic surface of the heart. Simultaneous unipolar precordial and esophageal leads were taken with a three-channel direct-writing Technicon Cardiograph. Using a right precordial V lead as the reference lead, it was possible to determine and compare the onset of the intrinsicoid ventricular deflections in Leads V_5 or V_6 and in the lower esophageal leads reflecting the potentials of the diaphragmatic and posterior aspects of the heart. Usually, Leads V_1 and V_6 were simultaneously recorded with each of the fifteen esophageal leads. In every case, unipolar leads were utilized to map the electrocardiographic topography above and below the standard positions of the V leads, including the left axilla and the upper abdomen. The onset of the intrinsicoid deflection in the precordial and esophageal leads in twenty persons with normal conduction was also determined. This group included twelve persons with left ventricular hypertrophy.

RESULTS

In left bundle branch block, the left ventricular cavity potentials recorded by esophageal leads at the atrial level were preponderantly positive, and the ventricular complexes were usually RS in configuration (Figs. 1 to 3). The R waves were slurred, notched, or bifid in character and of variable amplitude and were followed by an S wave, giving the appearance of equiphasic RS complexes. In nine of the fifteen cases, the esophageal electrocardiograms recorded at midatrial, upper atrial, and supracardiac levels revealed a minute Q wave preceding the ventricular RS pattern. This minute Q wave as seen in the left ventricular cavity potentials coincided with or preceded the R wave in the simultaneously recorded Lead V_1 (Fig. 1).



A.



B.

Fig. 1.—*A*, W. S., a 69-year-old man, with a left bundle branch block pattern. The QRS measures 0.14 second. *B*, W. S. Simultaneous precordial and esophageal leads. E_1 was recorded at diaphragmatic level. Note the intrinsic atrial deflection in E_3, the Q wave in E_3 to E_{14}, and the RS-T segment depressed in E_3 to E_{14}.

In every case of left bundle branch block, marked RS-T segment depressions were recorded in esophageal leads reflecting left ventricular cavity potentials (Figs. 1 to 3). These were associated with RS-T segment depressions recorded in the standard, precordial, and lower esophageal leads, the latter reflecting potentials of the posterior surface of the left ventricle (Fig. 2). In the left precordial leads, the T waves were usually inverted or diphasic in contour. In esophageal leads reflecting left ventricular cavity potentials, the T waves were usually diphasic, but, owing to the marked depression of the RS-T segment in these leads, an absolute correlation with the T waves in the left precordial leads was difficult.

In five of the cases of left bundle branch block, the esophageal leads reflecting the potentials of the diaphragmatic and posterior surface of the heart revealed ventricular complexes which were equiphasic in character with marked depression of the RS-T segment and diphasic or inverted T waves.

In the remaining ten cases of left bundle branch block, the ventricular complexes in the lower esophageal leads reflecting the posterior aspect of the heart were rS in configuration with elevation of the RS-T segment and upright T waves. These esophageal electrocardiograms resembled the patterns obtained in the right precordial leads (Fig. 2*A*). At higher esophageal levels, there was a transition zone wherein the R waves increased and the S waves decreased in amplitude until equiphasic RS complexes appeared at atrial level with depression of the RS-T segment and diphasic T waves.

The ventricular complexes recorded in Lead V_F in left bundle branch block were usually rS in configuration with isoelectric or slightly elevated RS-T segments and upright T waves. Multiple unipolar leads taken over the upper anterior left chest as high as the axilla revealed ventricular complexes resembling those seen in the left precordial leads. In the leads taken across the upper abdomen, the electrocardiograms obtained directly under the V_1 to V_3 positions consisted of rS complexes with slight elevation of the RS-T segment and upright T waves, while those recorded from below positions V_5 to V_7 showed Rs ventricular complexes with slight depression of the RS-T segment and inverted T waves. In leads placed about midway between the umbilicus and the xiphoid process, the electrocardiographic pattern was mainly rS in configuration with isoelectric or slightly elevated RS-T segments and upright T waves.

In the electrocardiograms of the twenty persons with normal conduction, the anterior surface of the left ventricle was activated from 0.01 to 0.03 second after the anterior surface of the right ventricle. In those electrocardiograms in which the lower esophageal leads revealed an R, Rs or qR pattern, the onset of the intrinsicoid ventricular deflections in the lower esophageal leads coincided with or appeared very slightly earlier (0.005 second) than that simultaneously recorded in V_6. In those electrocardiograms in which the lower esophageal patterns were rS in configuration, the onset of the intrinsicoid deflection, coincided with or occurred 0.01 to 0.02 second later than that seen in Lead V_1, but it was 0.005 to 0.03 second earlier than that simultaneously recorded in Lead V_6. In both of these groups, the onset of the intrinsicoid deflection in the esophageal electro-

cardiograms taken at a higher level, reflecting the posterobasal portion of the left ventricle, occurred 0.01 to 0.03 second later than in the simultaneously recorded Lead V_6.

In left bundle branch block, the anterolateral surface of the left ventricle was activated 0.08 to 0.10 second after the anterior surface of the right ventricle. In the five persons in whom the electrocardiograms recorded from the posterior aspects of the heart were mainly RS in configuration, the onset of the intrinsicoid deflection in Leads E_1 to E_4 occurred 0.04 to 0.07 second earlier than in Lead V_6

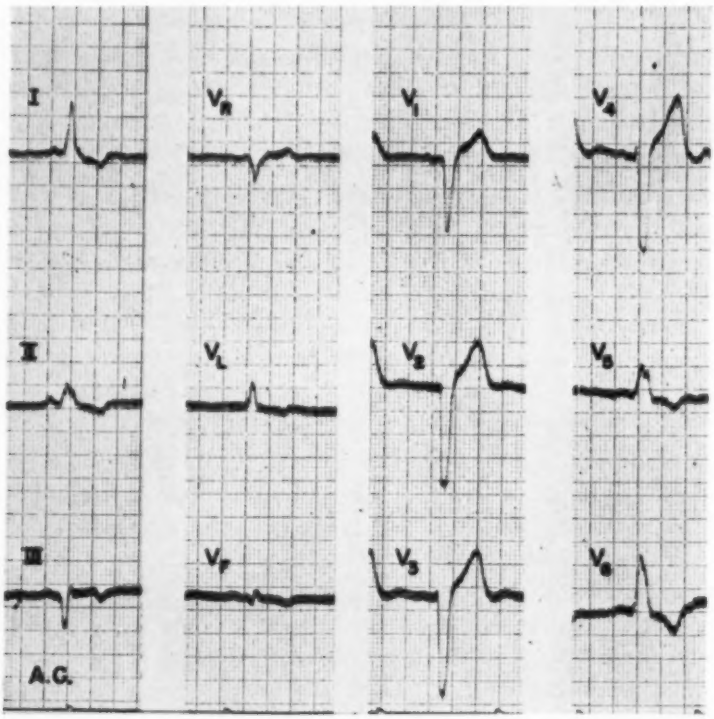


Fig. 2A.—A. C., a 70-year-old man, with a left bundle branch block pattern. The QRS measures 0.12 second.

(Fig. 1). In the esophageal leads recorded at higher levels, reflecting the posterobasal aspects of the left ventricle, the onset of the intrinsicoid deflection was 0.01 to 0.04 second earlier than in Lead V_6. In those cases of left bundle branch block in which the ventricular complexes in the lower esophageal leads were rS in configuration, the onset of the intrinsicoid deflection in the lower esophageal leads occurred 0.01 to 0.06 second later than in Lead V_1 and from 0.05 to 0.08 second earlier than in Lead V_6.

DISCUSSION

Left ventricular cavity potentials are recorded in esophageal leads at left atrial levels, the latter characterized by the presence of an atrial intrinsic deflection.[17,18] During normal conduction, including left ventricular hypertrophy,

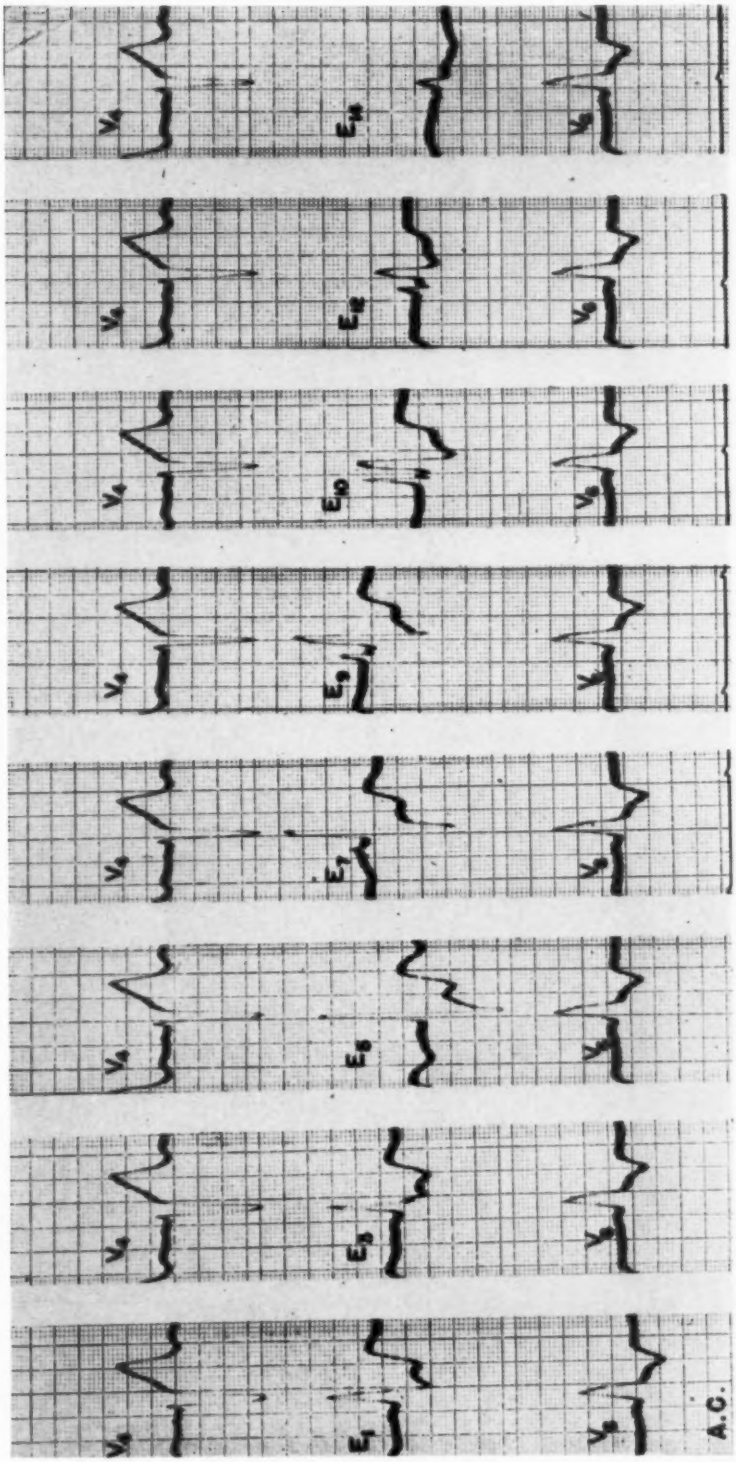
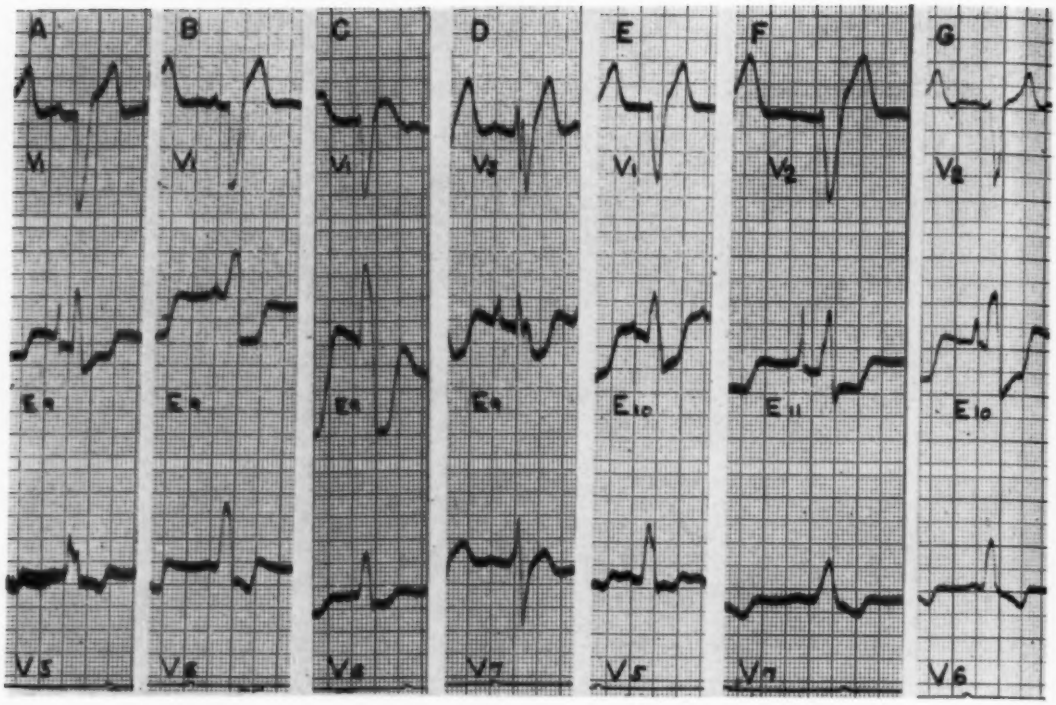
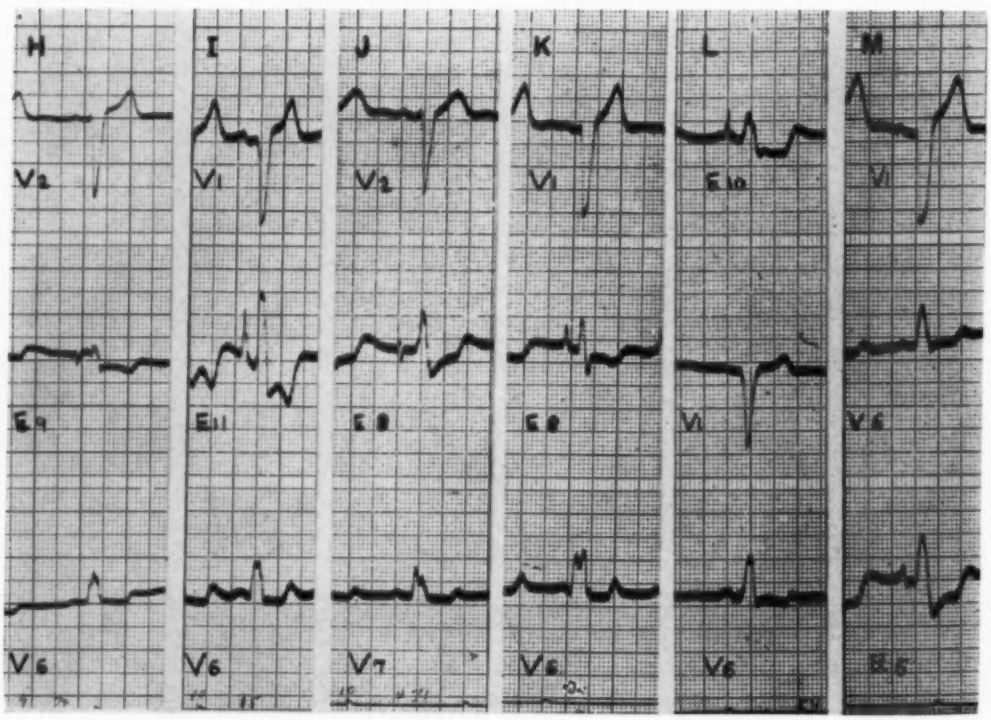


Fig. 2*B*.—A. C. Simultaneous precordial and esophageal leads. Note the intrinsic atrial deflection in E_9, the RS-T segment depressed in E_1 to E_{13}, and the RS pattern in E_1 to E_{13}.



A.



B.

Fig. 3,*A* and *B*.—Simultaneous precordial and esophageal leads at atrial level in twelve patients. Note the RS configuration and depressed RS-T segments in the esophageal leads.

the left ventricular cavity potentials were negative as evidenced by a QS pattern, the onset of the Q wave coinciding with or preceding the onset of any other deflection in simultaneously recorded leads.[18,20] In esophageal leads reflecting left ventricular cavity potentials, the RS-T segment was isoelectric in those instances in which the RS-T segment was also isoelectric in the precordial leads.[13] In left ventricular hypertrophy, the depressions of the RS-T segment recorded in left precordial leads and in lower esophageal leads, the latter reflecting left ventricular surface potentials, were consistently associated with RS-T segment elevations in esophageal leads reflecting left ventricular cavity potentials.[20]

From the data obtained in the present study, it is evident that in left bundle branch block, the left ventricular cavity potentials as recorded in esophageal leads at the atrial level were preponderantly positive as evidenced by an equiphasic RS complex rather than the QS pattern in normal conduction. These results are essentially similar to those of others who have recorded initial positivity by direct leads from the left ventricular cavity in experimental left bundle branch block in animals[10,11] and in left bundle branch block in man.[12]

Normally, the upper left portion of the ventricular septum is activated first,[2] and the electromotive forces produced by the spread of the excitation wave are directed away from the left ventricular cavity. As a result, the left ventricular cavity potentials are negative throughout the spread of the wave of accession as indicated by the QS pattern recorded inside the left ventricular cavity.[13,14] In left bundle branch block, the early positivity recorded inside the left ventricular cavity indicates that the electromotive forces at this time are directed toward this cavity. This indicates that the impulse probably spreads from right to left through the ventricular septum below the region of the block, rather than from left to right as in normal conduction. The deep S wave recorded inside the left ventricle probably represents the spread of the wave of accession through the left ventricular muscle from within outward.

In nine of the fifteen cases of left bundle branch block, there was a minute Q wave recorded at atrial level. This minute Q wave is probably due to the fact that the resultant vectorial forces are initially directed away from the left ventricular cavity. Another possible explanation for the presence of this minute Q wave is that the spread of the excitation process in the upper part of the septum proceeds as in cases of normal conduction. Sodi-Pallares, Thomsen, and Soberon[22] suggested that left-to-right activation of the septum may persist in some cases of left bundle branch block in which the left bundle is not involved above the level of the block. Their assumption was based on the finding of a small R wave inside the right ventricle in some cases of left bundle branch block. This observation has also been made by others.[23,24]

The electrocardiogram may be considered as the summation of the dextro- and levocardiograms.[2] Wilson and Herrmann,[6] by producing various degrees of asynchronism of the dextro- and levocardiograms in dogs, were able to produce multiple variations in the ventricular complexes from that of normal patterns to patterns of complete bundle branch block. In left bundle branch block, the asynchronism between the dextro- and levocardiograms due to the delayed activation of the left ventricle probably accounts for the altered configuration of

the QRS complexes and the RS-T segment depressions with inverted or diphasic T waves in the left precordial leads. The marked RS-T segment depressions and the T-wave configuration recorded from inside the left ventricular cavity by the esophageal leads at atrial levels may also be ascribed to the asynchronism of the dextro- and levocardiograms.

The simultaneous recording of the unipolar precordial and esophageal leads permitted the timing of the spread of the excitatory process in the ventricles. In the present study of twenty persons with normal conduction, the posterobasal surface of the left ventricle was activated 0.01 to 0.03 second later than the anterolateral surface of the left ventricle. This is in general accord with the observation of others in animals and man.[1-3]

In left bundle branch block, the diaphragmatic and posterior surface of the left ventricle was consistently activated 0.01 to 0.08 second earlier than the anterolateral surface of the left ventricle. The finding of RS ventricular complexes with deep S waves in the lower esophageal leads in left bundle branch block indicates that activity is still going on in the other portions of the heart after the impulse has reached the diaphragmatic and posterior surface. The earlier activation of the posterobasal surface of the left ventricle in left bundle branch block may be due to the anatomical location of the conduction system in the posterobasal portion of the septum.[2] Hence, the time required for the excitation process to spread from the right side of the septum to the posterior aspect of the left ventricle is shorter than to the anterolateral aspects of the left ventricle.

Recently, the opportunity presented itself in which the transition from normal conduction to that of left bundle branch block and vice versa could be recorded simultaneously in precordial and esophageal leads reflecting left ventricular cavity potentials.[25] In this case it was repeatedly demonstrated that the negativity of the left ventricular cavity during normal conduction changed to initial positivity as seen by the change from a QS to an RS pattern when varying degrees of left bundle branch block supervened. The RS-T segment was isoelectric during normal conduction and became markedly depressed in both the left precordial and esophageal leads, the latter reflecting left ventricular cavity potentials, when the conduction changed to left bundle branch block. The ventricular R pattern and the isoelectric RS-T segment in normal conduction in lower esophageal leads reflecting the diaphragmatic surface of the left ventricle were replaced by an equiphasic RS complex and a markedly depressed RS-T segment when left bundle branch block supervened.

It has been shown that the electrocardiogram recorded over the epicardial surface of a transmural infarct usually resembles the potentials in the adjacent ventricular cavity.[15,16] In normal conduction, a transmural infarction of the left ventricle may be diagnosed by the appearance of abnormally deep Q waves in the precordial leads. When a transmural infarction occurs in the presence of left bundle branch block, one would expect the precordial leads to resemble the electrocardiographic pattern found inside the left ventricle, namely, an equiphasic RS complex, and characteristic contours of the RS-T segment and T waves (Fig. 3).[10,26] However, one must be cautious in the interpretation of such a finding

since the characteristic pattern of left bundle branch block may only be recorded in the V_6 or V_7 position.

The differentiation of left ventricular hypertrophy from incomplete and complete left bundle branch block may be difficult in routine electrocardiograms. The finding of preponderant positivity in esophageal electrocardiograms reflecting left ventricular cavity potentials may serve as a readily available method for distinguishing incomplete or complete left bundle branch block from left ventricular hypertrophy.

CONCLUSIONS

1. Fifteen cases of left bundle branch block were studied with simultaneously recorded precordial and esophageal leads.

2. The left ventricular cavity potentials in these cases were preponderantly positive and consisted of equiphasic RS complexes with marked depression of the RS-T segments. In nine of the fifteen cases, a minute Q wave preceded the RS pattern.

3. In normal conduction, the posterobasal portion of the left ventricle was activated later than the anterolateral aspect of the left ventricle. In left bundle branch block, earlier activation of the posterobasal portion of the left ventricle occurred.

4. The significance of these observations is discussed.

We wish to express our appreciation to Dr. Arthur M. Master and Dr. Arthur Grishman for their cooperation in making this study possible.

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THE INTERRELATIONSHIP OF THE ELECTROCARDIOGRAPHIC COMPLEXES STUDIED BY SIMULTANEOUS MULTIPLE RECORDING

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UNIPOLAR precordial electrocardiography has been employed by numerous investigators to study clinically the electrophysiological changes of the heart under normal and pathological conditions.[1-10] Additional chest and endocardial leads in man and lower animals have been employed to correlate specific unipolar patterns with various pathological states. However, the simultaneous arrival of the depolarization impulse in various areas of the heart has been studied mainly on the exposed dog heart, and relatively little information on man is available.

Single standard leads have been taken simultaneously with a single chest lead, particularly in the early studies introducing the use of the precordial lead.[1-3] Simultaneous recordings of the three standard leads and Lead IV have been employed primarily by the Scandinavian workers.[11,12] More recently, Nahum and associates[12,14,15] have simultaneously recorded the three unipolar extremity leads with direct precordial leads in the dog. These workers have also related[16] the derivations of the standard leads to particular areas of the heart undergoing depolarization.

The present study was undertaken to gain further information regarding the course, rate, and conduction characteristics of cardiac depolarization phenomena in man. This report deals with the genesis and relationship of the various electrocardiographic deflections with one another.

SUBJECTS AND METHOD

Simultaneous recordings were made of six precordial unipolar leads, the three unipolar extremity leads, and the three standard leads in twenty-three normal subjects and thirty-three patients with various cardiac lesions. The group of normal subjects consisted of medical students and laboratory personnel without a past history of cardiac disease or cardiorespiratory symptoms of any type. The majority of the patients had been followed for long periods of time at the University of California Cardiac Clinic and the diagnosis in each case was well established.

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The electrocardiographic tracings were obtained through a six-channel electroencephalograph,* which was employed unchanged except for the addition of an attenuating network across the output of each of the power amplifiers to accommodate the galvanometers† in the recording oscillograph‡ with which all tracings were made. Centering controls were included in the attenuators for spacing the tracings on the recording paper. Electroencephalograph amplifiers have been used satisfactorily in the past for electrocardiographic registration.[17,18]

Each of the six channels operated independently of the other five amplifiers. The amplifiers were of the balanced type, and the first two stages of each were entirely battery operated to minimize hum and stray pickup. Each amplifier contained an eleven-step attenuator and a continuously variable gain control to regulate the size of the tracing. Appropriate filters were present for eliminating high- and low-frequency components of the input voltage as desired. The variable filters of the amplifiers were set to cause the least possible frequency discrimination. The time constant of the amplifiers in this arrangement was 0.8 second, permitting a slight but insignificant blunting of the peaks of the R wave. A 1 mv. square wave was provided for calibration purposes, and all six channels were calibrated simultaneously. Once set, the gain of the amplifiers was stable, and changing the position of the leads caused no change in the calibration. A sharply tuned filter was connected across each output to eliminate the 120 cycle voltage hum present in the power supplies. Each amplifier had a maximum gain of about 50,000,000. The leads from the patient were connected through a switching arrangement, permitting selection from eighteen channels. Two terminals were available for grounding the patient. When recording six precordial unipolar electrocardiograms simultaneously, the Wilson central terminal was the common ground for all amplifiers. The three standard and three unipolar extremity leads were also recorded simultaneously.

The six precordial unipolar leads were recorded simultaneously in all cases. The unipolar extremity and standard leads were recorded in two-thirds of those studied. Each record was taken at a speed of 3.6 cm. per second and also at the speed of 29 cm. per second. The high-speed record allowed more accurate measurements and easier comparisons between peaks of similar waves in different leads (Figs. 1 and 2). The error in measurement was estimated to be approximately 0.005 second.

RESULTS

Normal Subjects.—The values for the ventricular activation times (time from the beginning of the QRS complex to the peak of the abrupt downstroke of the R wave), QRS duration, and Q-T duration for the six precordial leads in normal subjects are presented in Table I.

In the twenty-two of twenty-three normal individuals in whom a determination was possible, the ventricular activation time for V_1 ranged from 20 to 44

*Grass Electroencephalograph Model IIA.

†Type 7-120, critically damped and linear in response from 0 to 500 cp., Consolidated Engineering Corporation, Pasadena, Calif.

‡Recording Oscillograph 5-101B, Consolidated Engineering Corporation.

milliseconds with a mean of 26.2 milliseconds and a standard deviation of 5.5. In V_6 the V.A.T. ranged from 32 to 67 milliseconds with a mean of 41.3 milliseconds and a standard deviation of 2.2. In two subjects (Table I, C. S. and P. M.) the V.A.T. was prolonged, being 0.044 second in V_1 (P. M.) with a duration of the QRS complex of 0.142 (although the M-shaped complex typical of right bundle branch block was not seen), while the V.A.T. in V_6 (C. S.) was 0.067 second with a QRS complex of 0.120 second. There was a marked difference in the duration of the QRS complexes and Q-T intervals in the different precordial leads. Occasionally, the QRS interval would differ as much as 50 milliseconds in the various leads in the same patient (Fig. 1). The QRS complex in normal subjects not infrequently exceeded 110 milliseconds in some of the precordial leads. The electrocardiographic patterns and contours were otherwise within accepted normal limits among all the normal subjects.

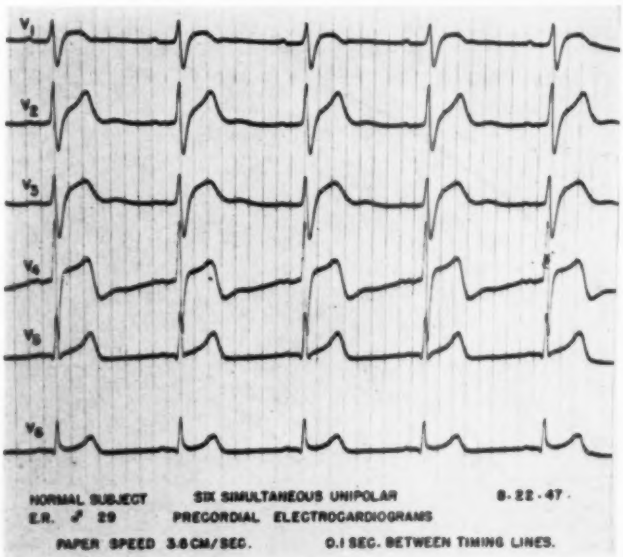

Fig. 1.—Six unipolar precordial leads recorded simultaneously in a normal subject. Note the asynchronous occurrence of homonymous peaks.

The peaks of the P waves in V_1 and V_2 when upright usually preceded those in V_5 and V_6 by 20 to 30 milliseconds in both the normal subjects (Fig. 2) and in the patients (Fig. 3). The interval from the end of the P wave to the onset of the QRS complex was greater in V_1 than in V_6. The negative phase of an inverted or diphasic P wave in V_1 was occasionally simultaneous with the peak of the P wave in V_6, particularly in the normal subjects.

Q waves in V_6 were present in twenty-one of the twenty-three normal subjects. The peak of the R wave in V_1 usually followed the nadir of the Q wave in V_6 in both groups (Figs. 1 and 2). The nadir of the Q wave in V_6 was simultaneous with the peak of the R wave in V_1 only when the R wave was very small. The nadir of the Q wave in V_6 was never later than the peak of the R wave in V_1 in any subject. The nadir of the S wave in V_1 and V_2 in the normal

TABLE I. DURATION OF COMPLEXES IN 23 NORMAL SUBJECTS

EXPERIMENT	MEASUREMENT	TIME (MILLISECONDS)						INITIAL WAVE IN V_6
		V_1	V_2	V_3	V_4	V_5	V_6	
E. R.	V.A.T.	30	25	25	28	35	38	Q
	QRS	105	105	108	81	64	65	
	Q-T	300	366	375	444	400	360	
O. M.	V.A.T.	28	28	33	32	38	36	Q
	QRS	105	107	105	89	85	55	
	Q-T	288	374	375	333	361	333	
B. S.	V.A.T.	23	22	35	40	45	45	Q
	QRS	108	94	73	72	95	100	
	Q-T	364	376	384	356	359	363	
E. F.	V.A.T.	25	22	23	33	41	40	Q
	QRS	109	109	83	81	62	62	
	Q-T	372	327	300	349	345	342	
B. J.	V.A.T.	29	33	37	49	52	52	Q
	QRS	100	94	99	109	78	84	
	Q-T	320	396	376	374	382	382	
H. B.	V.A.T.	21	22	31	47	53	46	Q
	QRS	120	120	105	73	97	91	
	Q-T	389	378	378	371	378	327	
C. M.	V.A.T.	21	22	24	32	43	46	Q
	QRS	105	112	94	90	97	100	
	Q-T	365	381	373	369	386	373	
I. S.	V.A.T.	24	36	40	42	35	49	Q
	QRS	109	106	88	90	75	108	
	Q-T	358	358	348	348	324	341	
S. M.	V A T.	23	26	36	32	38	35	Q
	QRS	107	105	93	91	86	82	
	Q-T	387	388	395	387	384	384	
B. S.	V.A.T.	21	23	26	43	43	45	Q
	QRS	126	126	125	109	82	72	
	Q-T	375	388	410	416	410	388	
M. S.	V.A.T.	20	27	45	51	54	50	Q
	QRS	112	100	80	110	117	110	
	Q-T	288	367	362	372	373	376	
V. H.	V.A.T.	29	29	55	56	53	56	Q
	QRS	86	130	102	110	105	111	
	Q-T	312	258	257	256	254	253	
M	V.A.T.	25	24	*	30	39	45	Q
	QRS	110	102	*	69	90	102	
	Q-T	450	360	*	450	450	450	
A. E.	V.A.T.	22	24	22	28	48	58	Q
	QRS	120	118	108	107	102	126	
	Q-T	309	325	326	357	367	363	
T. S.	V.A.T.	26	27	32	38	49	47	Q
	QRS	100	107	93	65	93	93	
	Q-T	369	392	392	379	385	385	

TABLE I.—CONT'D

EXPERIMENT	MEASUREMENT	TIME (MILLISECONDS)						INITIAL WAVE IN V_6
		V_1	V_2	V_3	V_4	V_5	V_6	
C. S.	V.A.T.	30	32	38	41	65	67	Q
	QRS	126	120	123	75	113	120	
	Q-T	?	340	343	336	350	346	
A. S.	V.A.T.	21	24	32	36	32	32	R
	QRS	108	101	96	95	89	84	
	Q-T	352	372	382	376	359	356	
J. M.	V.A.T.	31	32	47	51	51	50	Q
	QRS	117	106	84	104	106	106	
	Q-T	366	383	383	386	393	393	
P. M.	V.A.T.	44	41	46	39	58	51	Q
	QRS	142	141	142	76	115	111	
	Q-T	386	366	400	386	393	393	
S. M. Jr.	V.A.T.	31	29	36	42	43	43	Q
	QRS	112	108	69	102	110	110	
	Q-T	350	370	367	370	380	370	
E. V.	V.A.T.	20	21	28	38	30	34	Q
	QRS	98	107	110	100	75	92	
	Q-T	330	350	350	343	350	336	
H. L.	V.A.T.	0(QS)	16	28	30	31	27	R
	QRS	102	110	112	107	69	66	
	Q-T	340	373	373	360	353	350	
R. P.	V.A.T.	32	38	30	51	58	58	Q
	QRS	119	130	108	88	95	?	
	Q-T	?	352	332	341	341	?	

*Accurate measurement impossible.

subjects was usually 25 to 30 milliseconds later than the peak of the R wave in V_5 and V_6 (Figs. 1 and 2).

The peaks of the T waves did not occur simultaneously in the different precordial leads in the normal subjects (Fig. 1). The peaks of the T waves in V_1 and V_2 preceded the peaks in V_5 and V_6 by 20 to 30 milliseconds when the T wave in V_1 was upright. When the T wave in V_1 was inverted, as was often the case (Fig. 2), the peak of the T wave in V_2 always appeared first and the delayed peak of the T wave in V_6 and the nadir of the inverted T wave in V_1 were simultaneous.

All the normal subjects had either semivertical or predominantly vertical hearts as determined from the relationship of the unipolar extremity leads to the precordial leads. Consequently, the patterns seen in V_1 and V_6 were transmitted to the left arm and left leg, respectively, so that the onset of the intrinsic deflection occurred earlier in V_L than in V_F. Thus, the peaks of the R waves in the unipolar extremity leads were not simultaneous in these tracings in normal subjects (Fig. 5), except in the occasional subject with a semivertical heart in whom a small Q was also present in V_L.

The nadir of the QS complex in V_R was found to be simultaneous with the peak of the R wave in V_F in all except one of the normal subjects (H. L.). In this subject, the nadir of the QS complex appeared slightly before the peak of the R wave in V_F. The nadir of the QS complex in V_R preceded the nadir of the S wave (if present) in V_L when the heart was vertical in position. When the heart was in this position, the peak of the R wave in V_F preceded the nadir of the S wave in V_L again with the exception of the above case where the peaks were simultaneous.

Patients.—Measures of V.A.T. for V_1 ranged from 5 to 28 milliseconds with a mean of 17.7 and a standard deviation of 6.1 for the nineteen patients in whom the V.A.T. was not zero (QS) and where there was no evidence of right bundle branch block (Table II). For the six individuals with varying degrees of right

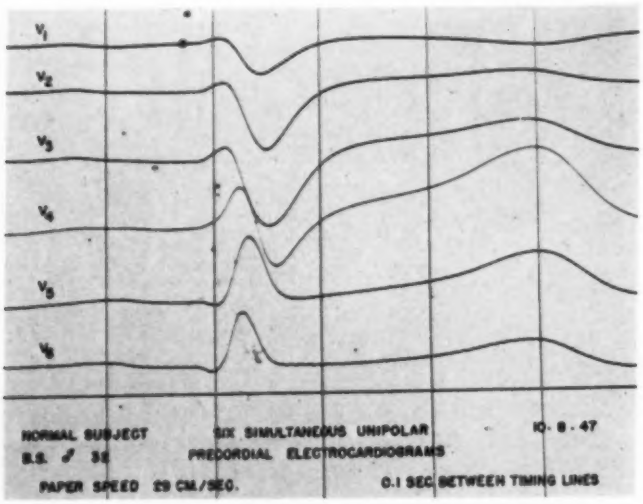

Fig. 2.—Six unipolar precordial leads recorded simultaneously at high speed in a normal subject.

bundle branch block the V.A.T. for V_1 ranged from 66 to 98 milliseconds. Measurement of the V.A.T. in V_6 ranged between 15 and 66 milliseconds with a mean of 44.3 and a standard deviation of 2.2 for the thirty-two patients in whom there was no evidence of left bundle branch block (Table II). The sole patient with left bundle branch block had a V.A.T. of 92 milliseconds in V_6. In the miscellaneous group of patients, therefore, the V.A.T. fell within normal limits except in those patients in whom lesions were present, such as left ventricular hypertrophy and bundle branch block, and in whom a prolonged V.A.T. was anticipated. A patient with coarctation of the aorta (W. S.), whose only prolonged V.A.T. occurred in V_4 (0.057 second), was found to have hypertrophy of the left ventricle at autopsy (2 cm. in thickness). This patient also had a very deep S wave in Lead V_2. The QRS complexes in the patients tended to be correspondingly prolonged whenever the V.A.T. was increased.

QS complexes were present in V_1 in one normal subject and four patients. The nadir of the QS complex was distinctly later than the peak of the R wave

TABLE II. DURATION OF COMPLEXES IN 33 PATIENTS WITH HEART DISEASE

EXPERIMENT	MEASUREMENTS	TIME (MILLISECONDS) V_1	V_2	V_3	V_4	V_5	V_6	INITIAL WAVE IN V_6	DIAGNOSIS
F. P.	V.A.T.	0(QS)	0(QS)	49	60	64	62	R	Left ventricular hypertrophy, auricular fibrillation
	QRS	123	130	126	126	120	109		
	Q-T	397	384	397	356	370	363		
I.	V.A.T.	12	14	19	35	44	47	R	Complete A-V dissociation, left ventricular hypertrophy
	QRS	101	100	93	99	65	91		
	Q-T	342	364	371	374	385	385		
F. M.	V.A.T.	93	54	54	50	40	40	R	Right bundle branch block
	QRS	150	82	121	121	107	107		
	Q-T	341	341	326	319	315	315		
M. C.	V.A.T.	17	20	24	35	42	37	Q	Normal electrocardiogram (arteriosclerotic heart disease)
	QRS	109	105	106	99	100	93		
	Q-T	349	384	401	404	385	373		
W. S.	V.A.T.	25	21	26	57	49	42	Q	Normal electrocardiogram (coarctation)
	QRS	104	108	114	104	101	95		
	Q-T	345	349	346	352	343	335		
J. J.	V.A.T.	0(QS)	0(QS)	8	16	73	65	R	Left ventricular hypertrophy
	QRS	128	126	121	134	117	128		
	Q-T	379	391	378	384	366	366		
J. R.	V.A.T.	0(QS)	10	40	65	53	51	R	Left ventricular hypertrophy
	QRS	106	125	118	115	110	108		
	Q-T	350	422	426	445	417	410		
P. C.	V.A.T.	12	21	38	38	46	48	R	Borderline ST changes and I.V. conduction defect (arteriosclerotic heart disease)
	QRS	109	116	130	128	130	129		
	Q-T	?	400	420	420	420	420		
E. A.	V.A.T.	66	32	37	37	33	33	Q	Incomplete right bundle branch block
	QRS	90	106	130	132	116	118		
	Q-T	350	350	400	384	384	346		
T. C.	V.A.T.	11	7	8	24	48	48	R	Old anteroseptal infarct
	QRS	92	90	98	87	96	109		
	Q-T	390	425	389	387	397	?		
J. C.	V.A.T.	76	31	33	41	37	36	R	Right bundle branch block
	QRS	124	124	124	125	72	71		
	Q-T	372	412	412	405	405	404		
J. C.	V.A.T.	28	29	37	40	41	49	Q	Normal electrocardiogram (aortic insufficiency)
	QRS	121	110	116	78	100	102		
	Q-T	328	393	386	376	369	372		
A. B.	V.A.T.	98					64		Right bundle branch block
	QRS	178					122		
	Q-T	400					390		
D. H.	V.A.T.	23	21	44	49	61	66	Q	Left ventricular hypertrophy
	QRS	117	119	116	94	117	125		
	Q-T	417	416	408	374	381	382		
C. B.	V.A.T.	25	26	28	30	43	40	R	Auricular fibrillation digitalis effect
	QRS	86	108	105	68	84	91		
	Q-T	322	290	257	?	?	?		

(*Table continued on next page.*)

TABLE II.—CONT'D

EXPERIMENT	MEASUREMENTS	TIME (MILLISECONDS) V_1	V_2	V_3	V_4	V_5	V_6	INITIAL WAVE IN V_6	DIAGNOSIS
B. C.	V.A.T.	17	20	26	27	29	29	R	Normal electrocardiogram (apical systolic click)
	QRS	92	100	92	58	68	67		
	Q-T	*	*	*	*	*	*		
E. P.	V.A.T.	21	27	26	27	22	32	Q	Normal electrocardiogram (patent ductus)
	QRS	102	100	55	89	66	84		
	Q-T	?	366	352	350	348	350		
G. P.	V.A.T.	69	Not recorded		43	NR	34	Q	Right bundle branch block
	QRS	116	Not recorded		117	NR	103		
	Q-T	?	Not recorded		394	NR	383		
C. F.	V.A.T.	107	91	82	37	40	23	R	Auricular fibrillation, complete A-V dissociation
	QRS	169	133	120	124	129	162		
	Q-T	383	365	359	364	414	414		
A. S.	V.A.T.	14	19	21	23	50	50	Q	Normal electrocardiogram (arteriosclerotic heart disease)
	QRS	89	97	113	109	100	100		
	Q-T	?	?	?	?	?	?		
S. L.	V.A.T.	18	19	20	56	53	51	Q	Borderline ST-T changes in extremity leads (congestive heart disease)
	QRS	105	111	108	109	108	108		
	Q-T	359	359	335	372	369	368		
T. B.	V.A.T.	23	23	29	36	42	42	Q	Auricular fibrillation digitalis effect
	QRS	71	108	113	67	90	87		
	Q-T	?	308	328	323	335	327		
E. S.	V.A.T.	76	79	72	76	67	41	R	Right bundle branch block, auricular fibrillation digitalis effect
	QRS	131	134	140	138	134	137		
	Q-T	?	?	?	?	?	?		
R. B.	V.A.T.	0(QS)	0(QS)	0(QS)	53	56	46	R	Normal electrocardiogram (rheumatic heart disease)
	QRS	76	76	70	110	109	92		
	Q-T	?	?	?	?	?	?		
P. G.	V.A.T.	5	6	24	29	36	34	R	Normal electrocardiogram (patent ductus)
	QRS	77	75	77	88	68	62		
	Q-T		334	349	348	347	334		
R. W.	V.A.T.	0(QS)	0(QS)	0(QS)	9	66	65	R	Left ventricular hypertrophy
	QRS	120	120	120	111	118	118		
	Q-T	422	439	446	432	?	?		
S. D.	V.A.T.	20	25	30	51	44	44	Q	Auricular fibrillation digitalis effect, ?early left ventricular hypertrophy
	QRS	101	111	104	84	97	98		
	Q-T		402	382	380	368	351		
D. M.	V.A.T.	0(QS)	0(QS)	0(QS)	14	13	15	R	Auricular hypertrophy, auricular premature beats, ventricular premature beats, blocked auricular premature beats
	QRS	112	112	114	104	104	106		
	Q-T	?	360	370	384	382	383		
I. S.	V.A.T.	0(QS)	6	26	30	24	28	R	Digitalis effect and myocardial changes secondary to coronary artery disease
	QRS	100	72	102	51	47	52		
	Q-T	332	298	332	?	309	309		
D. E.	V.A.T.	17	28	22	33	60	60	Q	Complete heart block
	QRS	122	122	133	77	100	122		
	Q-T	533	511	511	511	533	533		

TABLE II.—CONT'D

EXPERIMENT	MEASUREMENTS	TIME (MILLISECONDS) V_1	V_2	V_3	V_4	V_5	V_6	INITIAL WAVE IN V_6	DIAGNOSIS
A.T.	V.A.T.	12	15	22	22	32	44	R	Left ventricular hypertrophy, I.V. conduction defect
	QRS	138	138	147	138	109	100		
	Q-T	368	382	382	382	382	338		
R. M.	V.A.T.	11	23	21	23	92	92	R	Left bundle branch block
	QRS	127	147	151	158	158	151		
	Q-T	437	443	443	458	539	540		
M. B.	V.A.T.	26	39	39	39	42	50	R	Abnormal, no characteristic pattern
	QRS	124	126	122	122	85	105		
	Q-T	379	368	335	357	357	368		

*Accurate measurement impossible.

in V_5 or V_6 in the one normal subject and in two of the patients, one of whom exhibited the effects of digitalis and coronary disease and the other merely auricular abnormalities and a displaced transitional zone. The two remaining patients had left ventricular hypertrophy; in one the nadir of the QS complex in V_1 was simultaneous with and, in the other, slightly preceded the peak of the R wave in V_6. The nadir of the S wave in V_1 and V_2 in the patients showed that the peak of the R wave in V_5 and V_6 also preceded the nadir of the S wave in V_1 and V_2 except in those patients with bundle branch block or left ventricular hypertrophy.

QS complexes in Lead V_1 appeared in two of the six patients with definite left ventricular hypertrophy. In three of the remaining four the peak of the R wave in V_5 and V_6 was simultaneous with the nadir of the S wave in V_1 and V_2 (Fig. 4), while in the remaining patient the peak of the R in the left ventricular leads was slightly later than the nadir of the S in V_1 and V_2.

The peak of the R wave in V_6 coincided with the nadir of the S wave in V_1 (Fig. 3) in four out of five cases of right bundle branch block where there was an M-shaped QRS complex in V_1, considering the nadir of the "M" complex as the nadir of the S wave. The nadir of the S wave in V_6 was simultaneous with the peak of the R′ in V_1 in three of the patients, while in one patient the nadir of the S wave in V_6 was later than the peak of the R′. In this latter case, the peak of the R′ in V_R was also later than that in V_1 but appeared simultaneously with the nadir of the S wave in V_6. In the remaining case there was no S wave in V_6 for comparison.

The peaks of the T waves were appreciably delayed in bundle branch block in the leads overlying the ventricle with the defect in conduction; e.g., in right bundle branch block the peak of the T wave in V_6 appeared before the positive peaks of the diphasic T waves in V_1 and V_2.

Among the patients with right bundle branch block a prominent R′ in V_R was simultaneous with the nadir of the S wave in V_6. There was also a phase

difference in the peaks of the P and T waves in the different unipolar extremity leads, perhaps representing a reflection of the phase differences in these waves seen in the precordial leads.

The peaks of the waves in the standard leads also were not simultaneous (Fig. 5). This was true not only for the components of the QRS complexes but also for the P and T waves. The particular standard lead in which the peak of the wave came first, furthermore, was not constant but depended upon the changes in the various unipolar extremity leads.

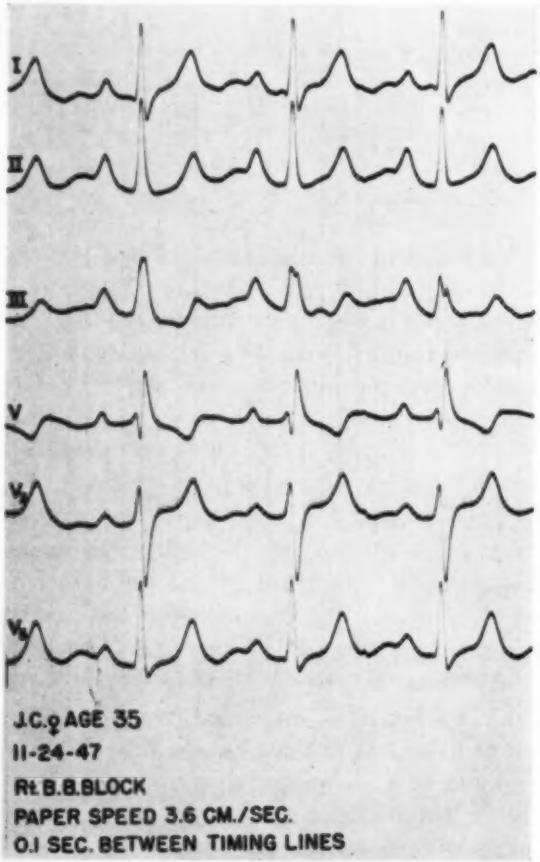

Fig. 3.—Three standard leads and three unipolar precordial leads recorded simultaneously in a patient with left ventricular hypertrophy. The nadir of the QS complex in V^1 occurs slightly before the R′ in V_1 occurs synchronously with the nadir of the S wave in left precordial leads and represents the intrinsic deflection (rather than the R wave). V refers to Lead V_1.

DISCUSSION

Marked differences in the duration of the QRS complex in the different precordial leads were found; in addition, the QRS complex was above 110 milliseconds in some leads. Part of this variation may be due to the difficulty of determining the exact point where the QRS complex ends and the ST segment begins in high-speed records. No galvanometer deflection occurs as the de-

polarization impulse travels parallel to the electrode; this may explain the late onset of the QRS complex in a particular lead. An isoelectric Q wave in those leads where the QRS interval is shortest may thus also be responsible. With two or three exceptions, the QRS interval was shortest in those leads (V_3 and V_4) lying over the septum, i.e., those leads without a small initial R or small initial Q wave, in which isoelectric Q waves could be postulated. However, it should also be noted that with few exceptions, the QRS interval was shorter in left

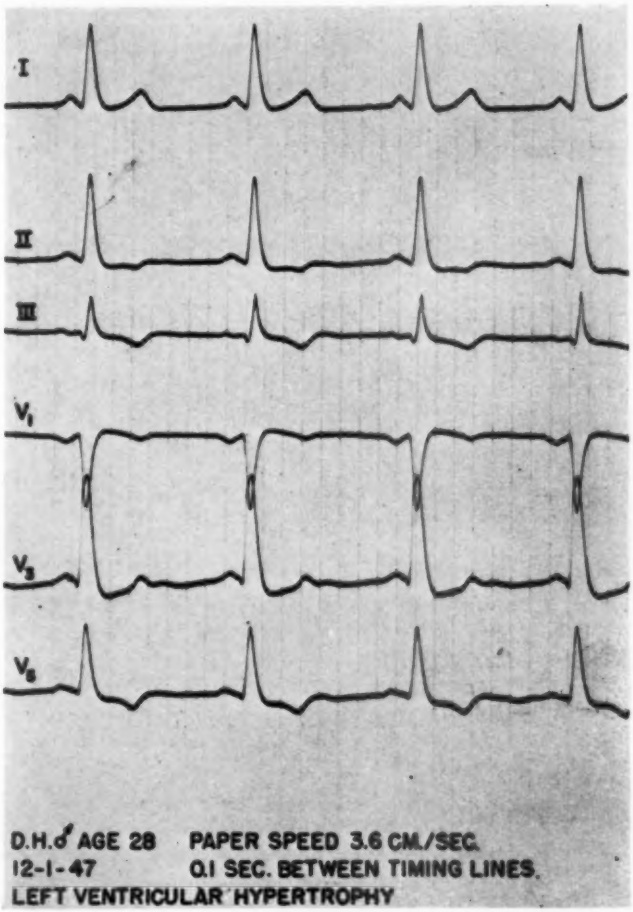

Fig. 4.—Three standard leads and three unipolar precordial leads recorded simultaneously in patient with left ventricular hypertrophy. The nadir of the QS complex in V_1 occurs slightly before the peak of the R wave in V_5.

ventricular leads (V_5 and V_6) than in the right ventricular leads (V_1 and V_2) despite the presence of an initial Q wave in V_5 and V_6. One must, therefore, postulate the presence of an isoelectric S wave besides an isoelectric Q wave to explain variations in the duration of the QRS complex in the different precordial leads.

The peak of the P wave in V_1 and V_2 usually preceded the peaks of the P waves in V_5 and V_6, possibly because the former electrodes faced a portion of the

auricles where the auricular intrinsic deflection occurs earlier than in that portion reflected by the V_5 and V_6 electrodes. Occasionally, a negative wave is inscribed in V_1 coincident with the peak of the P wave in V_6 and after the positive peak of the P wave is written in V_1. The negative portion of this diphasic wave is apparently produced by the predominance of the impulse passing away from the electrode through the left auricle; i.e., its mechanism appears to be similar to that by which the S wave is formed in V_1, although a PT_a wave is a possibility.

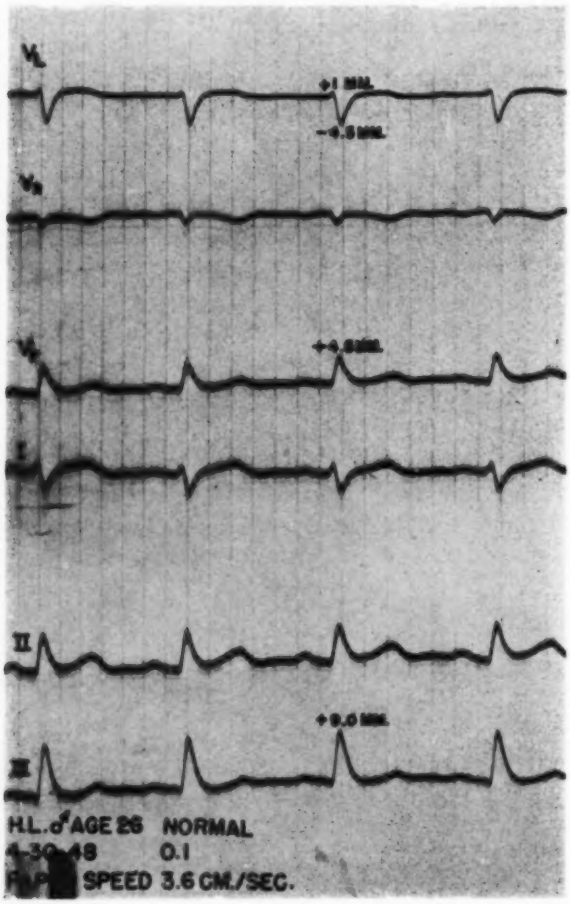

Fig. 5.—Three unipolar extremity leads and three standard leads recorded simultaneously in a normal subject. The asynchronous occurrence of homonymous peaks makes formulas for the calculation of the standard leads from the unipolar extremity leads inaccurate unless these leads are recorded simultaneously (see text).

When this voltage is equal to the impulse spreading through the rest of the right auricle, an isoelectric wave results after the auricular intrinsic deflection in V_1. This isoelectric period gives the impression that the interval from the end of the P wave to the onset of the QRS complex is greater in V_1 than in V_6.

The peak of the R wave in V_1, in general, occurred an appreciable interval after the nadir of the Q wave in V_6 in both the normal subjects and in the patients.

A perpendicular projected from the nadir of the Q wave in V_6 intersected the R wave in V_1 usually close to the peak, suggesting that the main portion of the R wave is contributed by the septum rather than the free wall of the right ventricle. The nadir of the Q wave in V_6 coincided with the R wave in V_1 in only a few cases, particularly when the R wave was very small. The R wave in these cases appears either to be wholly the result of septal depolarization or the result of dominance of the left ventricular potential so that the portion of the R wave contributed normally by the right ventricle is masked and an S wave results.

The nadir of the S wave in V_1 is thought to represent the arrival of the activation wave in the last portion of the left ventricle, and the peak of the R in V_6 signifies the arrival of the impulse beneath the electrode overlying that particular portion of the left ventricle (Wilson). However, the nadir of the S wave in V_1 and V_2 in all the normal subjects was an appreciable interval later than the peak of the R wave in V_5 and V_6. Thus, presumably, some portion of the left ventricle which is activated last is not detected by the usual left precordial leads, i.e., electrodes over V_5 and V_6 are not indicating the last part of the left ventricle to be activated. The delayed nadir of the S wave in V_1 and V_2 indicates that some other part of the left ventricle is being activated after the onset of the intrinsic deflection and the arrival of the depolarization wave under the electrodes in V_5 and V_6. This is supported by observations that Leads aV_F and aV_L may reveal changes not seen in V_5 and V_6. Lewis and Rothschild[19] indicated that the high lateral wall of the left ventricle was the last portion of this ventricle to be activated.

The same time relationships between the nadir of the S wave in V_1 and the peak of the R wave in V_6 were also found in the group of patients with the exception of those with bundle branch block and left ventricular hypertrophy. This exception was expected in bundle branch block where conduction through one of the bundles is considerably delayed, but the explanation in left ventricular hypertrophy is not clear. In three of four patients with left ventricular hypertrophy without QS complexes in V_1, the R wave in V_5 and V_6 was simultaneous with the nadir of the S wave in V_1 and V_2. The peak of the R wave in the left ventricular leads was slightly later than the nadir of the S wave in V_1 and V_2 in the remaining patient. One might expect the V.A.T. in V_5 and V_6 to increase with the thickened musculature in left ventricular hypertrophy.[20] However, the reason for failure of the time interval from the onset of the QRS complex to the nadir of the S wave in V_1 and V_2 to increase in left ventricular hypertrophy while the V.A.T. in V_5 and V_6 does increase is obscure. It is conceivable that only part of the left ventricle could hypertrophy, i.e., those portions beneath the fifth and sixth position electrodes, while the left high lateral wall remained unaffected. This would account for the increased V.A.T. in V_5 and V_6 with the time of onset of the QRS complex until the time of onset of the nadir of the S wave in V_1 and V_2 remaining approximately the same as in the normal subjects. A more likely explanation may be that in left ventricular hypertrophy the heart is rotated so that the electrodes at V_1 and V_2 no longer lie perpendicular to the high lateral wall of the left ventricle but instead lie more nearly perpendicular to those portions of the left ventricle detected by V_5 and V_6.

When QS complexes were present in V_1 in left ventricular hypertrophy, comparison with the peak of the R wave in V_6 showed that these waves appear in time more like an S wave than a Q wave; i.e., in left ventricular hypertrophy the nadir of the QS complex in V_1 was either simultaneous with or immediately before the peak of the R wave in V_6. QS complexes in V_1 were also timed as S waves in the normal group or in cases other than left ventricular hypertrophy and bundle branch block; i.e., the nadir of the QS complex in V_1 was distinctly later than the peak of the R wave in V_5 or V_6.

The maximum nadir of the M–shaped complex in V_1 coincided with the peak of the R wave in V_6 in patients with right bundle branch block. This would appear to indicate that the S wave in V_1 in right bundle branch block is caused by the impulse passing through the left ventricle as stated by Wilson and coworkers.[3] The relationship between the S wave in V_6 and R′ in V_1 indicates that in right bundle branch block the peak of the R′ represents the onset of the intrinsic deflection rather than the peak of the R wave. The one case where the nadir of S_{V6} was slightly later than the peak of the R′ in V_1 but simultaneous with the peak of the R′ in V_R suggests that right exploratory leads might have found an area where the intrinsic deflection or peak of the R′ would have been later than that in V_1 and perhaps simultaneous with the nadir of S wave in V_6. The coincidence of the peak of the R′ in V_R with the nadir of the S wave in V_6 was not limited to right bundle branch block but was found whenever an S wave was present in V_6 and an R′ was present in V_R. This confirms similar findings in dogs and would appear to indicate that the last portion of the ventricles to be activated is actually the right ventricle near the conus.

The peak of the T wave in V_1 was earlier than the peak of the T wave in V_6 when all the T waves were upright. This was expected since repolarization should be delayed in those leads where the intrinsic deflection or depolarization is latest. This viewpoint was further supported by the observation that the positive peaks of the T waves were appreciably delayed in bundle branch block n the leads over the ventricle with the block.

An inverted T wave in V_1 has been interpreted as due to prolonged systole in the outer muscle layers of the right ventricle.[21] The simultaneous occurrence of the peaks of the inverted T_{V1} and the upright T_{V6} suggests that the electrode over V_1 is predominantly detecting repolarization changes over the left ventricle in these cases.

The observation that the peaks of the R waves in the different unipolar extremity leads were not simultaneous makes the use of the formulas for predicting the standard leads from the unipolar extremity leads inaccurate unless all the leads are taken simultaneously. If one assumes that the voltage of the R wave in Lead III is equal to the voltage of the R wave in V_F minus that of the R wave in V_L (Lead III $= V_F - V_L$ in millimeters), one may be incorrect. To predict accurately the voltage of the R wave in Lead III, one must record simultaneously and project a line up from the peak of the R wave in Lead III until it intersects V_L and V_F and use the values at the points of intersection rather than at the peaks. In Fig. 5, the voltage of the R wave in Lead III is equal to +9.0 mm., that in V_F is equal to +4.5 mm., and that in V_L is equal to +1.0 mm.

(Lead III $= +4.5 - 1 = +3.5$ mm.). This is obviously incorrect since the voltage of the R wave in Lead III is equal to +9.0 mm. If one now substitutes in this formula the values at the point of intersection of a line projected up from the peak of the R wave in Lead III to where it intersects V_L and V_F, the formula becomes Lead III $= +4.5 - (-4.5) = +9.0$ mm. or the correct value. This principle, of course, holds true for any wave or point which one wishes to calculate.

The nadir of the QS complex in V_R was found to be simultaneous with the peak of the R wave in V_F in the normal subjects. Furthermore, the nadir of the QS complex in V_R preceded the nadir of the S wave in V_L whenever the position of the heart was vertical and an S wave was present in V_L. Thus, the QS complex in V_R appears to be a reflection of the passage of the impulse through the left ventricle, since the peak of the R wave in V_6 preceded the nadir of S_{V1}. There was one exception (H. L., Fig. 5), in whom the nadir of the QS complex in V_R came slightly before the peak of the R wave in V_F and in whom the nadir of the S wave in V_L was simultaneous with the peak of the R wave in V_F rather than later as in the other normal subjects. The explanation for this one discrepancy is not clear.

A phase difference was noted in the peaks of the P and T waves in the different unipolar extremity leads which may be a reflection of the phase differences in these waves seen in the precordial leads. The standard leads also showed a lack of homonymous peaks among the different waves which were of no constant pattern but reflected the asynchronism present in the unipolar extremity leads.

SUMMARY

1. The use of simultaneous recordings of six electrocardiographic leads in twenty-three normal subjects and in thirty-three patients with a variety of cardiac lesions has afforded the opportunity of studying the genesis of the different waves through comparison of simultaneous peaks.

2. Study of the precordial leads (V_1 through V_6) revealed the following:

A. There is a considerable variation in duration of the QRS complexes in the various precordial leads.

B. Peaks of the P and T waves occurred consistently earlier in V_1 than in V_6 unless the waves were inverted, in which case the peaks tended to be simultaneous.

C. Among the normal subjects, as contrasted to the patients with left ventricular hypertrophy and bundle branch block, the R wave in V_5 and V_6 did not represent the last portion of the left ventricle to be depolarized.

D. QS complexes in right ventricular leads were essentially similar in time to S rather than Q waves.

E. The peak of the R′ in bundle branch block represents the onset of the intrinsic deflection.

3. Study of the unipolar extremity leads and the standard leads revealed the following:

A. There is a phase difference between the peaks of the P, Q, R, S, and T waves in the various standard leads.

B. The peak of the R wave in the unipolar extremity leads was usually not simultaneous, particularly among normal subjects.

C. The QS complex in V_R was similar in time to an S rather than a Q wave.

D. With a vertical heart, the nadir of the S wave in V_L followed the peak of the R wave in V_F; the nadir of the S wave in V_1 followed the peak of the R wave in V_6.

E. A phase difference in the peaks of the P and T waves existed in the different unipolar extremity leads.

F. Formulas for deriving the standard leads from the unipolar extremity leads are only approximations unless the leads are taken simultaneously.

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THE NATURE OF LEFT AXIS DEVIATION IN CONGENITAL CARDIAC DEFECTS WITH RIGHT VENTRICULAR HYPERTROPHY

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THE most frequent electrocardiographic findings in congenital heart disease with right ventricular hypertrophy are right axis deviation in the standard leads, as determined by the potentials in the extremity leads, and the pattern of right ventricular hypertrophy in the precordial leads. At times, right bundle branch block, either partial or complete, may be seen in patients with hypertrophy of the right ventricle. In such cases, the standard leads may show left axis deviation, but the precordial leads will indicate the nature of the conduction defect. On the other hand, left axis deviation without right bundle branch block is rarely seen in congenital defects with right ventricular hypertrophy.

In the era of "standard lead" electrocardiography, rare cases of right ventricular hypertrophy with left axis deviation were reported. In a case of tetralogy of Fallot, Calo[1] recorded left axis deviation, nodal rhythm, and incomplete right bundle branch block. In his review, Schnitker[2] reported left axis deviation in two patients of the tetralogy group and in one patient with persistent truncus arteriosus. In one of the patients with tetralogy of Fallot, left axis deviation was associated with a probable right bundle branch block. These cases were considered exceptions to the diagnostic rule that patients with congenital heart disease and right ventricular hypertrophy showed right axis deviation. An explanation for these exceptions was sought empirically by correlating the axis deviation in the standard leads with the relative size of the ventricle. This explanation was recently invoked by Gasul and associates[3] in a case of tetralogy of Fallot and patent foramen ovale with left axis deviation.

Recent electrocardiographic studies have shown that axis deviation depends not only on ventricular size but also on the position of the heart relative to the extremities. The left axis deviation in Burchell's[4] case of interatrial septal defect and in Mannheimer's[5] case of tetralogy of Fallot was shown to be dependent on the extremity potentials. In his report of congenital aortic atresia and left axis deviation, Soloff[6] also explained the left axis deviation on the basis of cardiac position. The electrocardiographic findings in our three cases of interatrial septal defect with left axis deviation further elucidate the nature of left axis deviation

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in the presence of right ventricular hypertrophy. Moreover, the intracardiac potentials recorded by us in patients with congenital and acquired right ventricular hypertrophy contribute to the better understanding of cardiac position in chamber hypertrophy and its effect on the extremity potentials.

METHOD AND MATERIAL

Three patients with interatrial septal defect and left axis deviation were studied. The diagnosis in each patient was based on the physical findings, x-ray examination, angiocardiography, and cardiac catheterization.

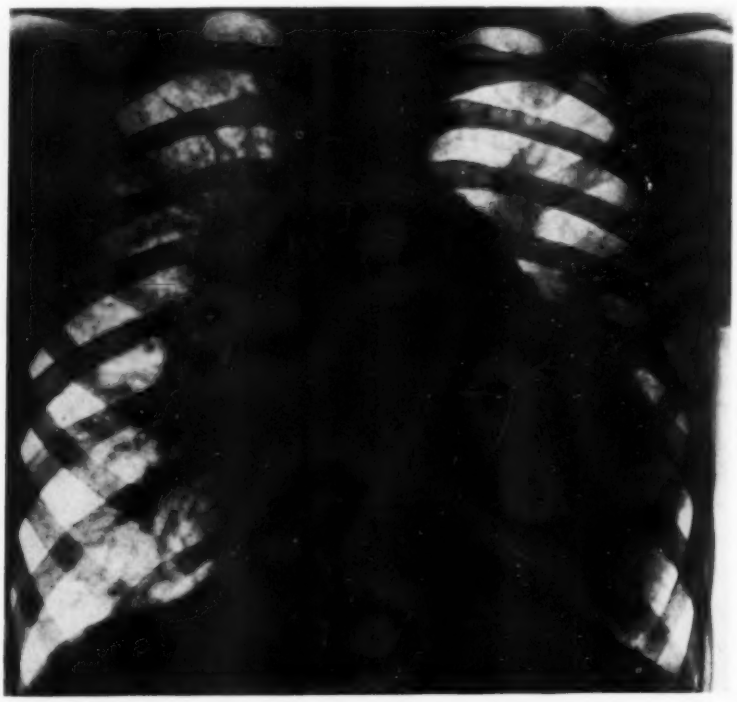

Fig. 1.—Roentgenogram of I. B. The heart is enlarged to the right and left with rounding of the apex and broadening of the waist. The pulmonary artery segment is prominent; the hilar branches are enlarged. The aortic arch is small.

The intracardiac potentials were recorded after cardiac catheterization of the pulmonary artery. The significant data were obtained from three patients with acquired right ventricular hypertrophy (pulmonary heart disease) and two patients with congenital right ventricular hypertrophy (tetralogy of Fallot).

1. *Patient I. B., a White Girl, 7 Years of Age.*—The deviation of the electrical axis was to the left. The S_3 was very deep and greater than the R_3. A Q_1 was present, and the T_1 was inverted. The R wave in aV_L was very tall and was preceded by a deep Q wave and followed by an inverted T wave. The R wave in aV_L was taller than the R wave in aV_F. The ventricular complex in aV_L resembled the complex over V_5 and V_6 (Figs. 1 and 2).

2. *Patient M. B., a White Boy, 3 Years of Age.*—The deviation of the electrical axis was to the left. A q_1 and s_1 were present. A broad R′ was recorded in aV_R. The R in aV_L was taller than

the r in aV_F and was preceded by a q. The ventricular potential in aV_L resembled most closely the potential recorded over the left precordium (V_5 to V_7). The ventricular complex over the right precordium showed a delayed positive R′ and suggested a delay of conduction in the right ventricle. The QRS was not widened; it measured 0.08 second. There was no evidence for the interpretation of chamber hypertrophy (Figs. 3 and 4).

3. *Patient I. C., a White Woman, 28 Years of Age.*—The deviation of the electrical axis was to the left. The extremity leads were normal, as were the precordial leads (Figs. 5 and 6).

Intracardiac Potentials.—In patients with right ventricular hypertrophy, congenital and acquired, a characteristic pattern was often recorded in the pulmonary artery just above the pulmonic valve. An initial small r wave preceded an s wave which was then followed by a delayed tall R′, which in turn was occasionally followed by an s′. The T wave was negative.

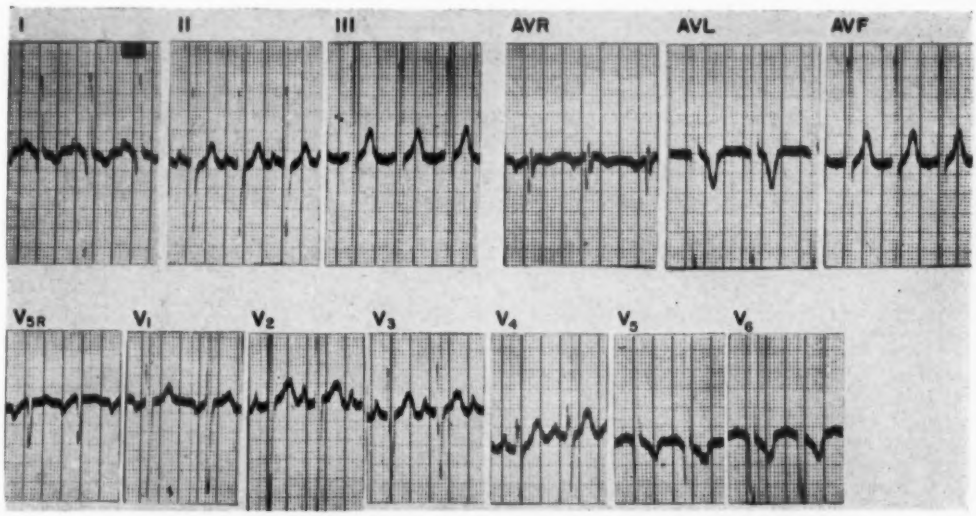

Fig. 2.—Electrocardiogram of I. B.: left axis deviation. The QR in aV_L may represent an rsR′ similar to the pattern illustrated in Fig. 7, *A* and *C*. Similarity of aV_L to V_5 and V_6 indicates an unusual rotation.

The records in Fig. 7 illustrate this finding. *D* and *E* are records from two patients with tetralogy of Fallot. The rsR′ in the pulmonary artery was recorded simultaneously with V_1, which does not show an R or R′. *A* is a record from a patient with pulmonary heart disease. The characteristic rsR′ was recorded simultaneously with V_1 which it does not resemble and with aV_R which it does resemble. The r in this record is very small. If the standardization were the usual 10 mm. per 1 mv., the r would not be seen and the pattern would be interpreted unsuspectingly as a qR. *C*, a record from a patient with pulmonary heart disease, shows the r in the intrapulmonary lead but not in V_1. In V_1 the r is isoelectric, and an erroneous interpretation of a qRs could easily be made. *B*, a record from a patient with pulmonary heart disease, demonstrates again the presence of typical rsR′s′ in the intrapulmonary lead and its absence in V_1.

DISCUSSION

The axis deviation in the standard leads is determined by the extremity potentials, because the standard leads actually represent the difference of the potentials between two extremities. In the literature there are but two cases of right ventricular hypertrophy and left axis deviation which include extremity and precordial leads. In Mannheimer's[5] case of tetralogy of Fallot with left axis deviation, a q_1 and s_1 were present in the standard leads. The QRS was

widened to at least 0.12 second. What appeared to be a delayed R′ was seen in V_R. There was what appeared to be a deep Q and tall R in V_L. The R in V_L was greater than the r in V_F. Of course, this resulted in left axis deviation in the standard leads. The s in Lead I was determined by the delayed positivity in V_R. The QRS complex in V_F showed an rS and resembled V_5 and V_6 where an rS pattern was also seen. The right side of the precordium (V_1 to V_4) showed an R preceded by what appeared to be a q wave and followed by an s wave. The T wave was inverted in V_1 and V_2. The V_L potential resembled the potential over the right precordium. The tall R wave and inverted T wave over V_1 and V_2 and the deep S waves over V_5 and V_6 were considered correctly to be characteristic of right ventricular hypertrophy. Since V_L resembled the potentials over the right precordium and V_F the potentials over the left precordium,

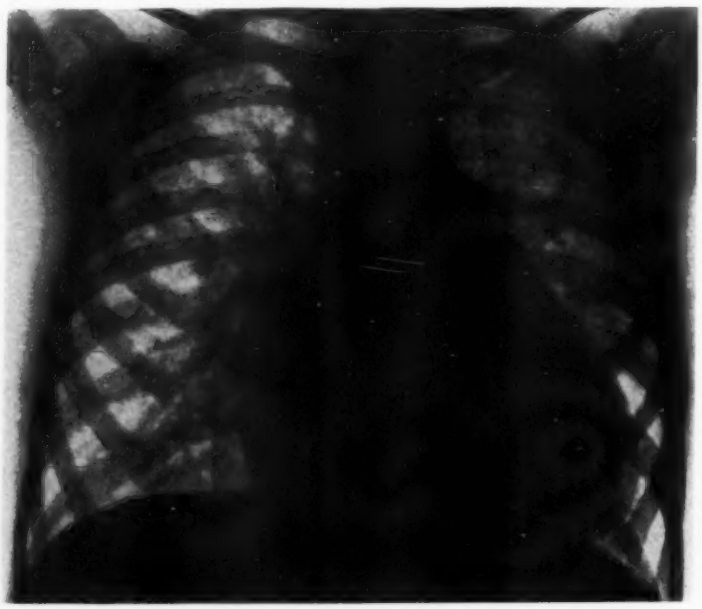

Fig. 3.—Roentgenogram of M. B. The heart is enlarged to the right and left with broadening of the waist. The pulmonary artery and its branches are prominent. The aortic arch is small.

the heart was considered to be in a vertical position (Wilson). It was also implied that the positivity (tall R) in V_L was derived from the right ventricle. Mannheimer believed that the unusual vertical position of the heart determined the left axis deviation.

In Burchell's[4] case of interatrial septal defect with left axis deviation, a q_1 and s_1 were present in the standard leads. The aV_R showed an rsR′ pattern with a late R′. The late R′ in aV_R accounted for the s_1. There was an rS in aV_F, which most closely resembled V_1. The R in aV_L was preceded by a q wave. It was this R in aV_L which determined the left axis deviation. The precordial leads were not diagnostic of right ventricular hypertrophy. An rS was seen in V_1, and the QRS complexes from V_2 to V_6 seemed to be biphasic. In comparing

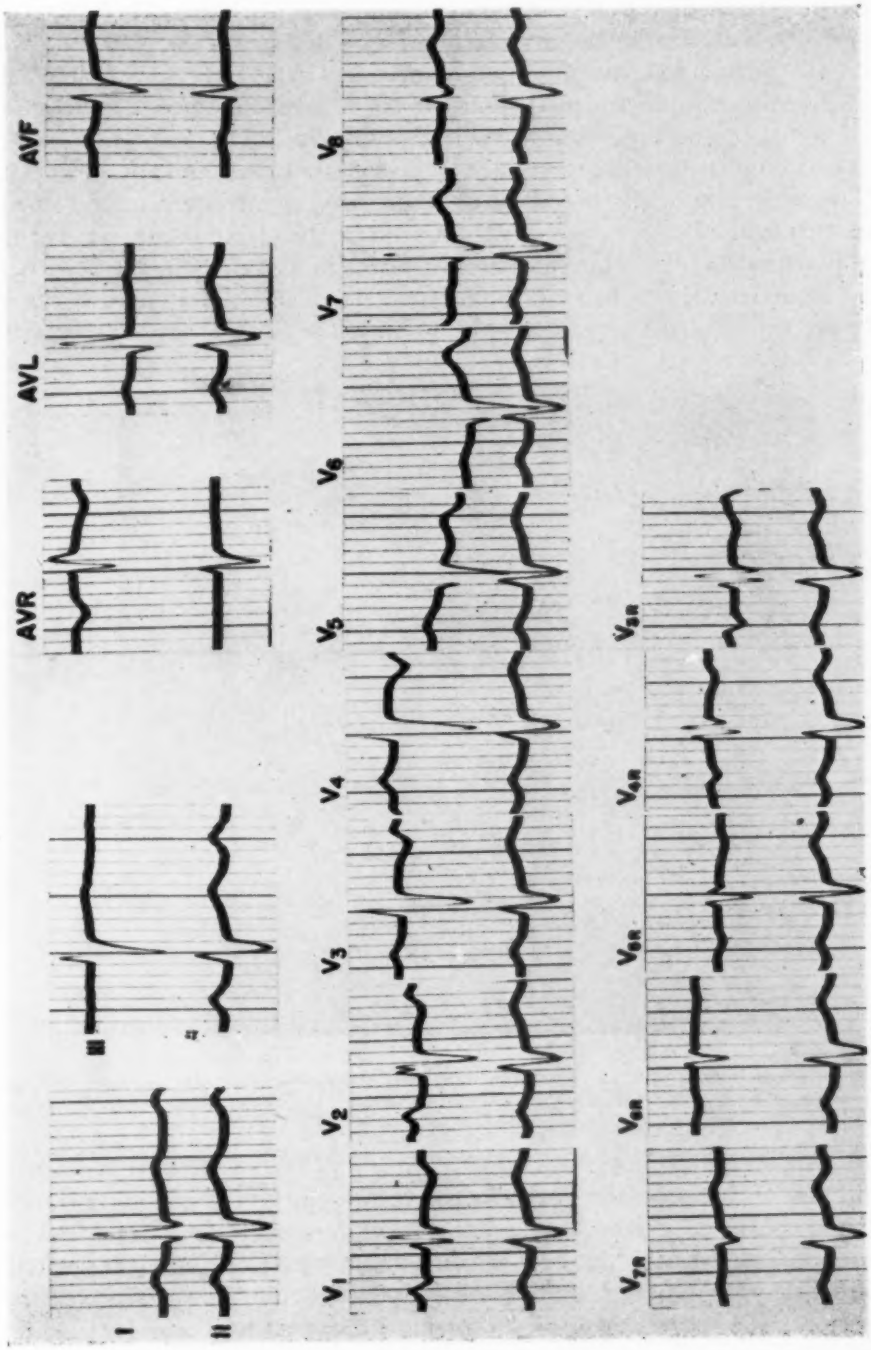

Fig. 4.—Electrocardiogram of M. B.: left axis deviation. The delayed R′ in V_{4R}, V_{3R}, and V_1 indicates mild conduction delay in the right ventricle which may be associated at times with right ventricular hypertrophy.

this case with one of right ventricular hypertrophy and right axis deviation. Burchell noted that the aV_R potentials (rsR′) were similar in both cases. In the case of right ventricular hypertrophy with right axis deviation, the positivity (tall R) was in aV_F, and in the case with left axis deviation, the positivity was in aV_L. In the unusual case of right ventricular hypertrophy with left axis deviation, the assumption was made that the tall R represented right ventricular potential and that it was reflected to the left arm instead of to the foot.

There is no question that the positivity in V_L determines the left axis deviation. The two cases in the literature and our cases of interatrial septal defect illustrate this fact. The problem that remains to be elucidated is the origin of the positive potential in V_L. Mannheimer and Burchell assumed that it is derived from the right ventricle. Theoretically, however, this positivity (tall R wave) could be derived as a surface potential from either the right or the left ventricle.

Fig. 5.—Roentgenogram of I. C. The heart is slightly enlarged to the right and left. The pulmonary artery and its branches are prominent. The aortic arch is small. Klippel-Feil deformity of the cervical spine is present.

The reflection of this potential to the foot, resulting in right axis deviation, or to the left arm, resulting in left axis deviation, will depend on the anatomical and electrical relationship with the extremities of the hypertrophied right ventricle and its surface potential and the normal left ventricle and its surface potential. Theoretically, this relationship can be further influenced by the degree of right ventricular hypertrophy and its effect on the position of the left ventricular surface.

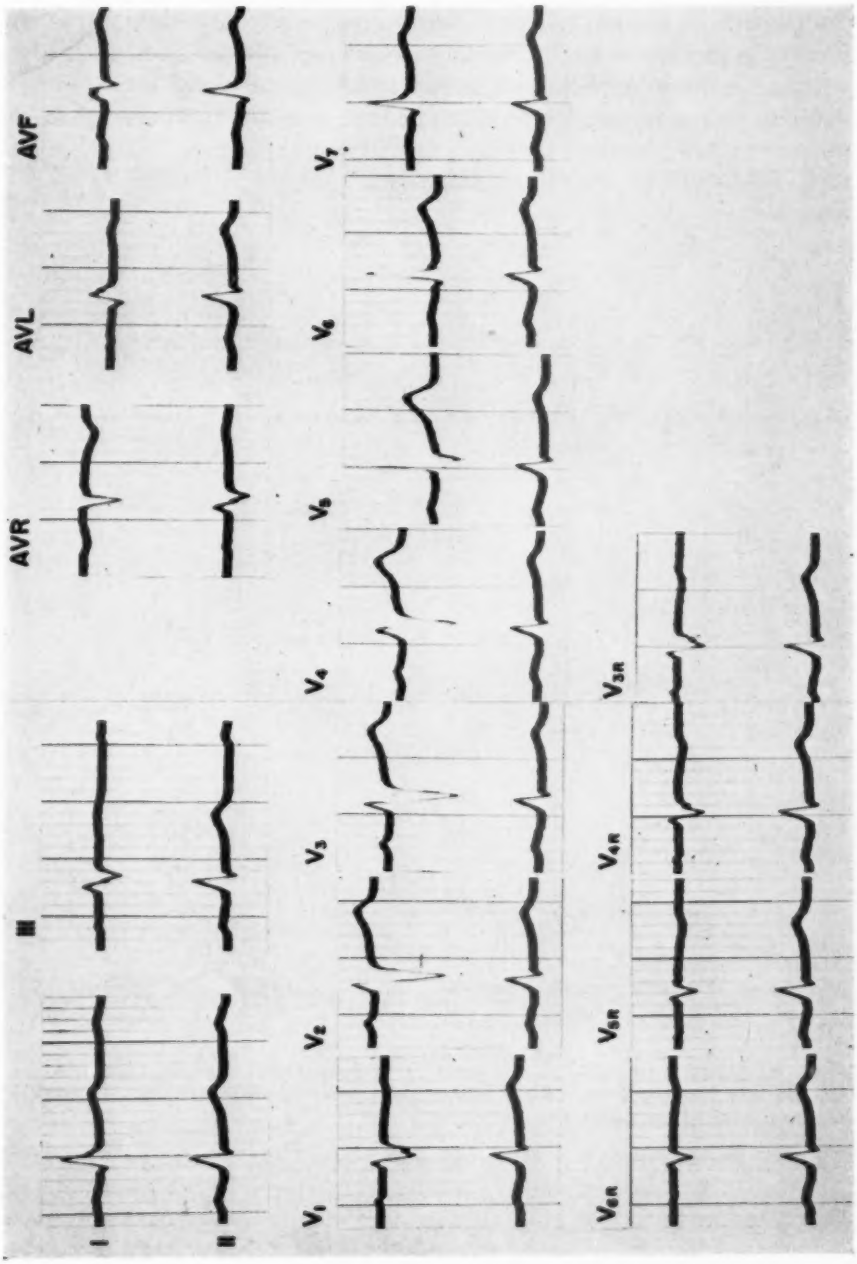

Fig. 6.—Electrocardiogram of I. C.: left axis deviation. The electrocardiogram is normal.

Our studies of right ventricular hypertrophy, both acquired and congenital, contribute further information toward the interpretation of data presented in this paper and in the literature. The diagnosis of right ventricular hypertrophy in our cases is made on the basis of the clinical diagnosis, x-ray examination, angiocardiography, and the electrocardiogram. The precordial leads on the right side (V_1 and aV_R) may or may not show the tall R usually associated with right ventricular hypertrophy (Fig. 7). When one explores the right side of the heart

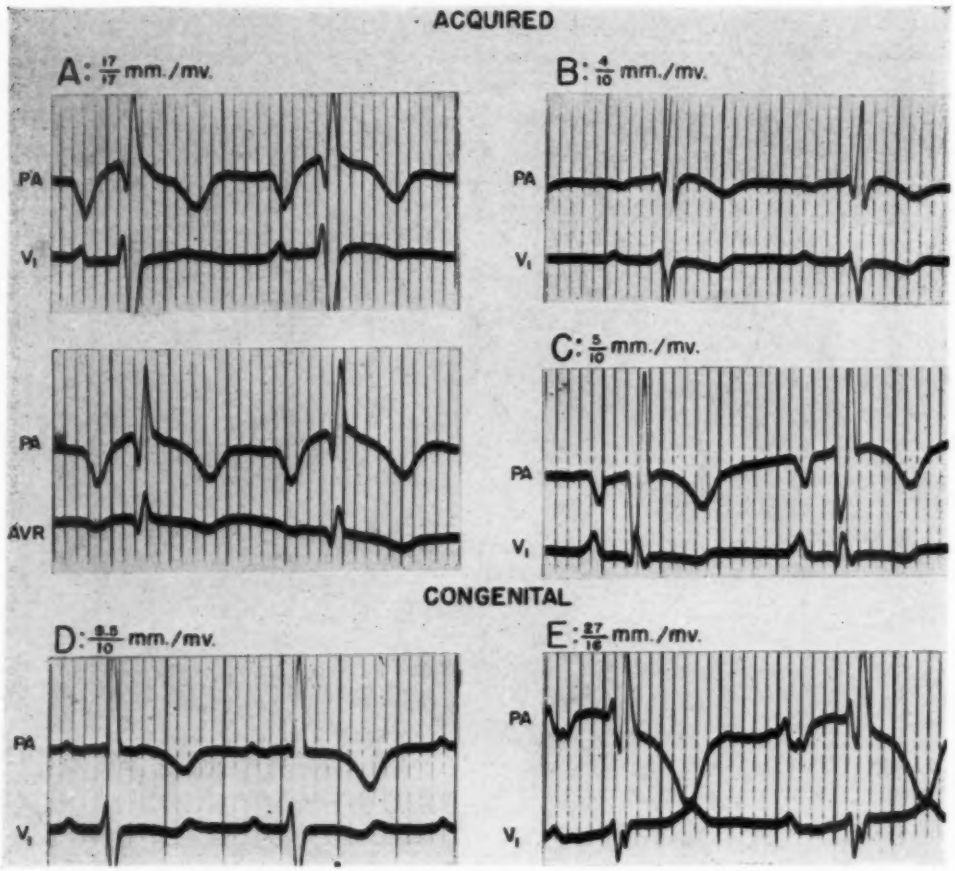

Fig. 7. Intracardiac potentials in congenital and acquired right ventricular hypertrophy. The rsR's' complex with inverted T wave is the characteristic potential recorded with the electrode in the supravalvular portion of the pulmonary artery (*PA*).

in these latter cases, the predominant positivity (R) is found in the pulmonary artery just above the pulmonic valve (Fig. 7). The initial small r may be of low amplitude or isoelectric, and then the pattern resembles a qRs (V_1 in Fig. 7,*C*, *PA* and aV_R in Fig. 7,*A*). The terminal s may at times be isoelectric or absent (*PA* in Fig. 7,*D*). This potential of predominant positivity (rsR's') is similar in configuration to the potentials recorded in aV_R and V_1 in cases of right ventricular hypertrophy (Fig. 7). It is not obtained in the cavity of the right ventricle but

may be recorded in the cavity of the right atrium.[7] Such a potential is recorded only in regions near the surface of the right ventricle. Whether a true qR pattern (not preceded by an isoelectric r) can be derived at the right ventricular surface in hypertrophy is problematical, but theoretically possible. In any event, our data on the intracardiac potentials in right ventricular hypertrophy indicate that predominant positivity which is encountered at V_1 and aV_R (rsR′s′ and its modifications) is often obtained in the pulmonary artery just above the pulmonic valve. In normal hearts, the potential recorded above the pulmonic valve does not show the tall delayed R which is seen in right ventricular hypertrophy.[7] Thus, in all likelihood, the recorded positivity (rsR′s′) in the pulmonary artery just above the valve reflects the predominant potential of the hypertrophied right ventricle. In right ventricular hypertrophy, this potential may be reflected to the left arm (aV_L) because of elevation and displacement of the pulmonary artery to the left secondary to hypertrophy. With these considerations in mind, the electrocardiographic findings in our cases and in those of the literature may be further analyzed.

In all likelihood, the qR pattern in V_L and over the right precordium in Mannheimer's[5] case of tetralogy was derived from the right ventricular surface. The initial r in this instance was probably isoelectric, and the pattern resembled the V_1 of record *C* in Fig. 7, an apparent qRs which is really an rsR′s′ complex with an isoelectric r. The tall R in V_L can therefore be a reflection of the pulmonic conus surface potential, its deflections being recorded by an electrode in the supravalvular portion of the pulmonary artery. This potential may at times be reflected to the left arm because of elevation of the pulmonic conus and artery cephalad and to the left in right ventricular hypertrophy.

The origin of the small Q, tall R pattern in the aV_L lead of Burchell's case of interatrial septal defect is difficult to determine because the precordial leads were bizarre.

Our cases are different from Mannheimer's case in that the aV_L potential resembled the left rather than the right precordium. In patient I. B., the QR pattern in aV_L may actually represent an rsR′ pattern such as is found above the pulmonic valve in right ventricular hypertrophy. The presence of this pattern over V_5 and V_6 instead of over the right precordium indicates a peculiar rotation. Like Mannheimer's patient with tetralogy of Fallot,[5] the tall R in aV_L of our patient I. B. with interatrial septal defect is probably a reflection of right ventricular surface potential to the left arm.

The electrocardiographic findings in patient I. C. may be regarded as normal. There was left axis deviation without evidence of chamber hypertrophy in either the extremity or precordial leads. The qR in aV_L was similar to the qR in V_6 and V_7 and was a reflection of left ventricular surface potential as is the case in a normal electrocardiogram. In this case of interatrial septal defect the left axis deviation was that of a normal electrocardiogram.

In patient M. B. (Fig. 4) the rSR′s′ pattern in V_{4R} to V_1 was indicative of a mild conduction delay in the right ventricle; an S was present in V_6, V_7, and V_8. The qR in aV_L did not resemble the characteristic surface pattern of right ventricular hypertrophy as recorded in the pulmonary artery (rsR′s). It resembled

the qRs over the left precordium which is a reflection of left ventricular surface potential. In this patient with interatrial septal defect and right ventricular hypertrophy, a mild conduction delay in the right ventricle was associated with left axis deviation.

It is evident that left axis deviation in right ventricular hypertrophy is determined by predominant positivity in the left extremity potential. In some instances (Mannheimer's patient and patient I. B.), this positivity is derived from the right ventricular surface and is reflected to the left arm from the region of the conus. In other instances (patients I. C. and M. B.), the left axis deviation is not associated with an hypertrophy pattern. In patient I. C. the electrocardiogram was normal. In patient I. B., the electrocardiogram was normal except for the mild conduction delay in the right ventricle. In these latter instances, the right ventricular hypertrophy had no electrical representation in the electrocardiogram. The positivity in the left arm was a reflection of the left ventricular surface potential, as it is in patients with normal hearts and left axis deviation.

The variability of the electrocardiographic findings in these patients with right ventricular hypertrophy indicates that rotation and position of the heart are more crucial than chamber hypertrophy alone in the determination of the extremity potentials and, hence, the axis deviation.

SUMMARY

1. The electrocardiogram of interatrial septal defect and tetralogy of Fallot without complicating hypertensive or syphilitic heart disease may show, on rare occasion, left axis deviation despite right ventricular hypertrophy.

2. Positivity (tall R or R′) in the V_L lead greater than the positivity in the V_F lead determines the left axis deviation.

3. Intracardiac potentials in congenital and acquired right ventricular hypertrophy indicate that the predominant positivity in V_L may be derived from the right ventricular surface.

4. In some instances, the left ventricular surface potential may determine the positivity in V_L.

5. The variability of the electrocardiographic findings in our cases of interatrial septal defect indicates that rotation and cardiac position are more important than chamber hypertrophy alone in the determination of the extremity potentials and, hence, the axis deviation.

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VECTORCARDIOGRAMS OBTAINED IN PATIENTS WITH RIGHT VENTRICULAR HYPERTROPHY WHOSE ELECTROCARDIOGRAMS DISPLAY AN UNUSUAL AXIS DEVIATION OR LEFT AXIS DEVIATION. IV.

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DURING the course of an investigation of the vectorcardiogram and electrocardiogram in patients with congenital heart disease, a small number were found who displayed left axis deviation in the presence of marked hypertrophy or enlargement of the right ventricle. Unusual axis deviations, that is, those lying between plus 180 degrees and minus 90 degrees in the triaxial reference system were observed in a somewhat larger number of such patients. The substance of this report consists of a vectorial analysis of these two groups. It is unnecessary to state that the vast majority of all patients who were known to have cardiac anomalies associated with right ventricular hypertrophy showed the expected "right axis" deviation, i.e., an electrical axis lying between plus 90 degrees and plus 180 degrees.

Though much has been written about the electrocardiogram in congenital heart disease and about the relationship between right axis deviation and right ventricular hypertrophy, little attention has been paid to these few paradoxical and bizarre cases. Only a few acceptable cases of left axis deviation in the presence of hypertrophy of the right ventricle have been recorded.[1-8] These have all been patients with congenital heart disease.

Bizarre axis deviations which result in predominantly downwardly directed QRS complexes in all three standard leads have been reported in four groups of patients. In addition to patients with congenital heart disease, such an electrocardiogram has been observed in those with myocardial infarction,[9,10] cor pulmonale, [10,11,12] and rheumatic involvement of the mitral valve.[13] We believe that the vectorcardiograms to be reported here, which were obtained in patients with congenital heart disease, will be similar to those found in advanced cor pulmonale because marked right ventricular hypertrophy is common to both. This group has not been studied extensively as yet. Vectorial analysis of the results of myocardial infarction has been reserved for another publication. Vectorcardiographic analysis of ventricular depolarization, i.e., the QRS complex alone, will be presented in this report.

A discussion of the technique and theoretical considerations of vectorcardiography has been presented previously.[14] Briefly, the vectorcardiogram is a visualization of the time course of the instantaneous electrical axes of the heart. The sum of the electromotive forces produced by the action currents of the heart at every instant during depolarization and repolarization is a vector quantity.

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As such, it has magnitude, sense, and direction and is symbolized by an arrow. The length of the arrow represents the mean, manifest magnitude of the electrical forces at that instant, and its direction is that of the mean direction of force. A line connecting the distal tips of all the arrows which represent the vector sums of the forces of accession will form a loop. This loop is the vectorcardiogram. This spatial heart vector is three dimensional. It is registered on three

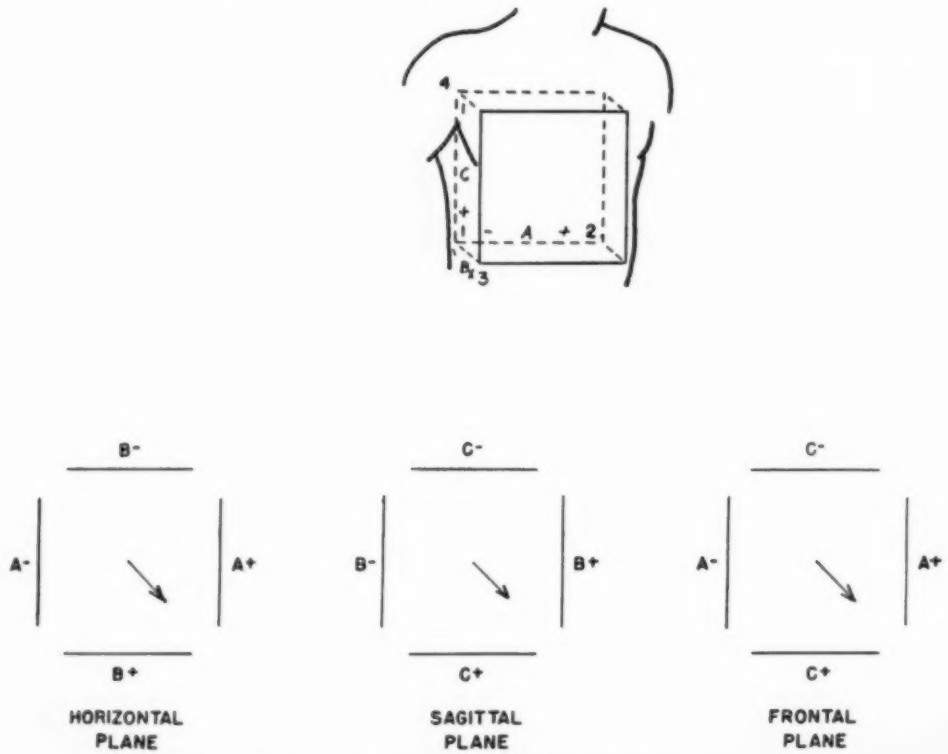

Fig. 1.—The lead arrangement and polarity are shown as seen by the observer.

oscilloscopes as its simultaneous projection in the horizontal, sagittal, and frontal planes. The standard leads and unipolar chest leads are derivatives of the frontal plane vectorcardiogram, and the unipolar precordial leads similarly are intimately related to the horizontal plane vectorcardiogram.[15] Complexes obtained from bipolar leads are scalar projections of the cardiac vector along the line between the two electrodes. Unipolar lead complexes result from projection of the central vector upon a line connecting the electrode with the electrical center of the heart.

MATERIAL AND METHODS

All patients were obtained for study from the clinics and wards of The Mount Sinai Hospital. They were all studied by the authors. The diagnoses and the presence of right ventricular hypertrophy were established by use of fluoroscopy and clinical findings in all cases, by angiocardiography in all but one case, and by cardiac catheterization in three cases. The position of the ventricles was grossly

estimated from the fluoroscopy and angiocardiogram. Vectorcardiograms were obtained by photographic reproduction of an oscilloscopic image of the frontal, sagittal, and horizontal plane vector loops simultaneously. A Technicon electrocardiograph and vectorscope were employed. Electrocardiograms were taken at four times the usual speed (10 cm. per second) unless specifically noted. The vector loop was interrupted 400 times per second by intensity modulation to permit a time analysis.

In all the illustrations, the horizontal, sagittal, and frontal plane vector loops are found in that order, reading from left to right. Arrows indicate the direction of rotation. The polarity and lead arrangement are indicated in Fig. 1.

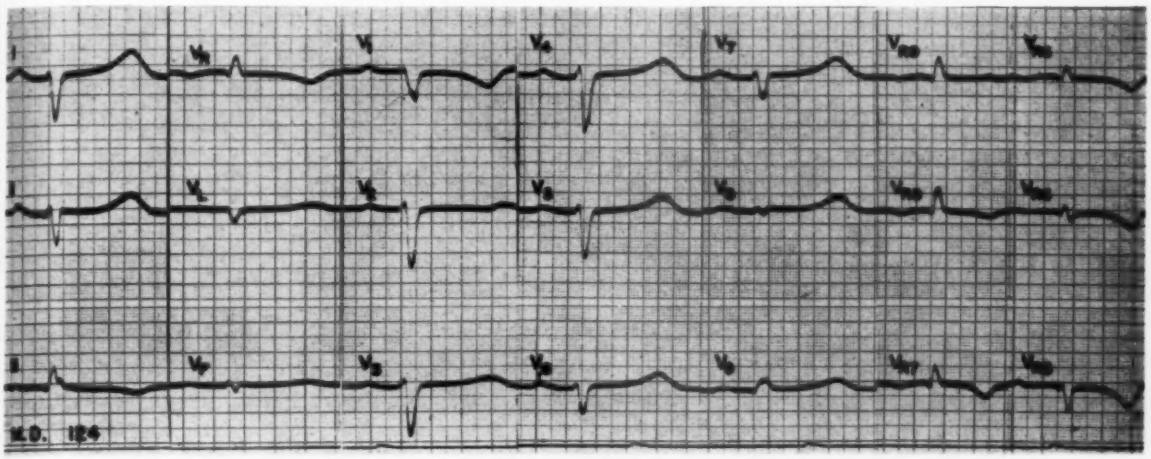

Fig. 2*A*.—Electrocardiogram of M. D. with quadruple speed, showing right axis deviation and small r, deep S waves in Leads V_{R5} through V_7.

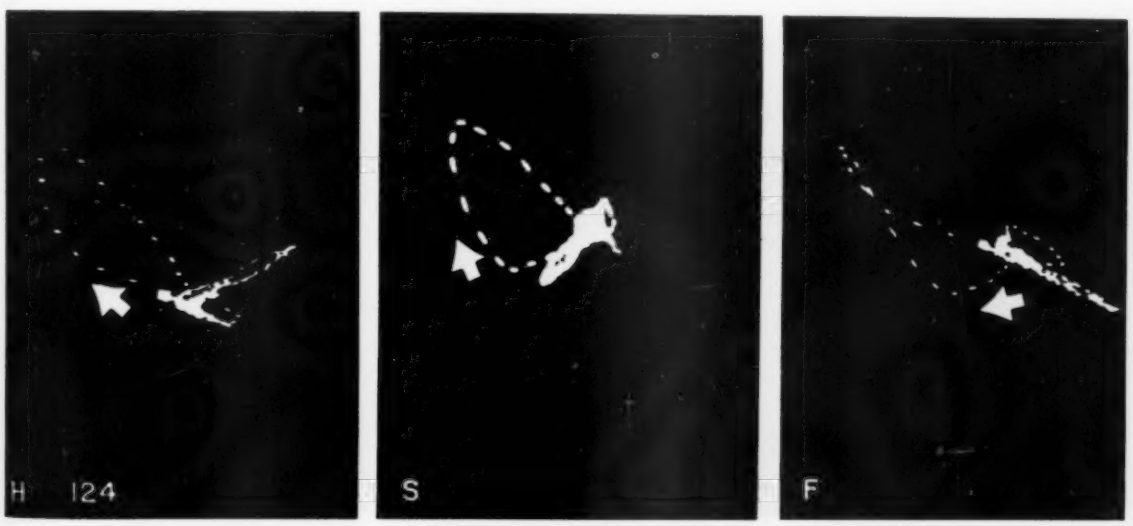

Fig. 2*B*.—Vectorcardiogram of M. D., showing clockwise rotation in all three planes and an orientation of the main loop in the right lower, posterior octant.

RESULTS

1. Unusual Axis Deviation.—

CASE 1.—M. D. was a 29-year-old, white woman whose probable diagnosis was tetralogy of Fallot with interatrial septal defect. The presence of right ventricular hypertrophy was ascertained by fluoroscopic examination and visualization of a large right ventricle and right atrium by angiocardiography. The other angiocardiographic findings of an interatrial communication, early visualization of the aorta, and small pulmonary vascular markings confirmed the diagnosis. The electrocardiogram, seen in Fig. 2*A*, shows marked right axis deviation. There is a tall, late R wave in Lead V_R. Leads V_F and V_L do not closely resemble any precordial leads. The un-

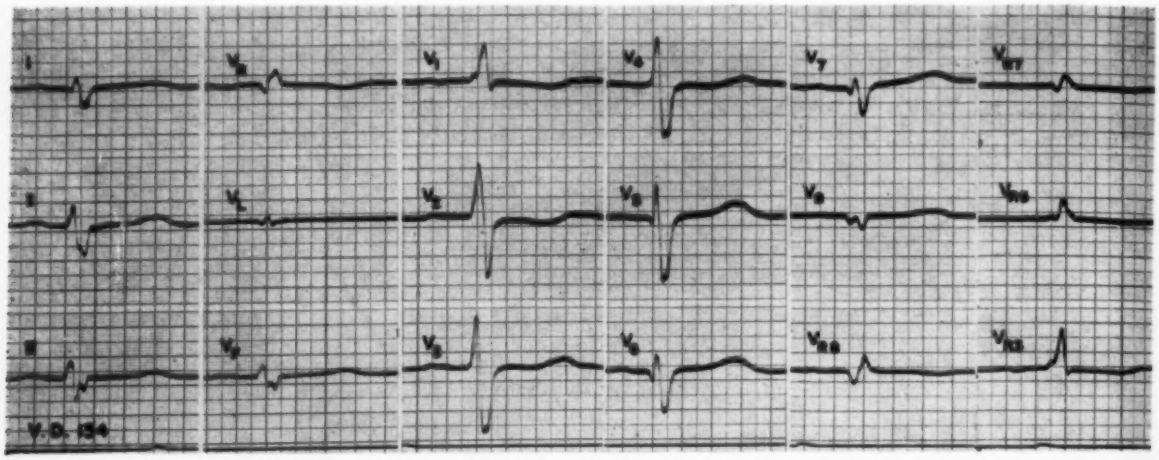

Fig. 3*A*.—Electrocardiogram of V. D. with quadruple speed, showing predominantly negative deflections in the standard leads and a precordial pattern characteristically associated with right ventricular hypertrophy.

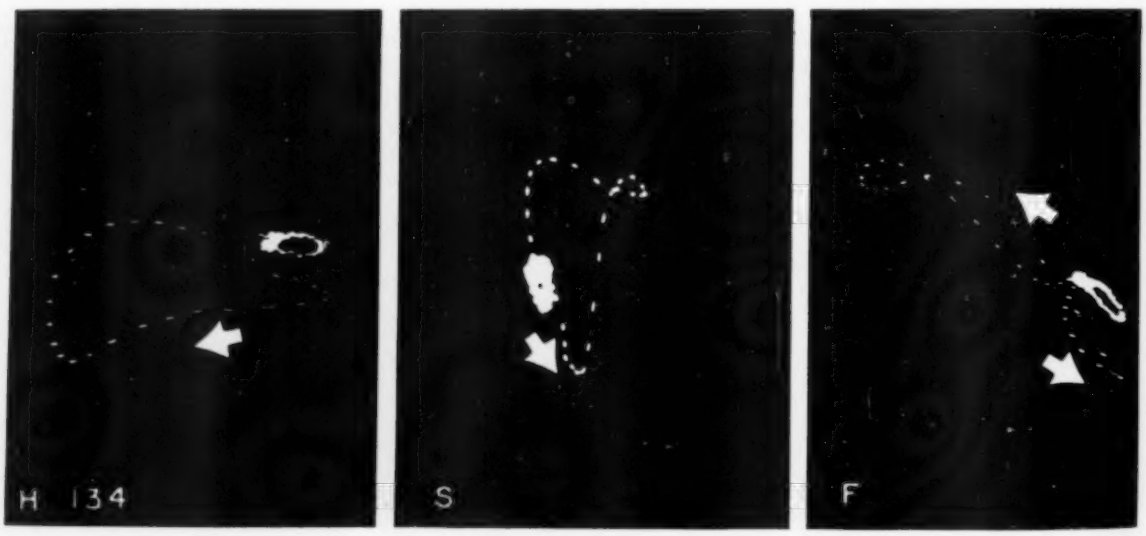

Fig. 3*B*.—Vectorcardiogram of V. D., showing an initial orientation to the left and downward and a final orientation of the major portion of the loop in the right upper, anterior octant.

usual feature is the presence of small r, deep S waves across the entire front of the chest from V_{R3} through V_8. It is only in the right posterior quadrant that tall R waves appear. The vectorcardiogram is seen in Fig. 2*B*. The frontal plane vector loop begins with a short segment which proceeds upward and to the right. This is believed to be the result of septal forces. The centrifugal limb then turns sharply to the right, proceeds laterally in a clockwise direction, reaches its peak, and returns sharply to the isoelectric point. The horizontal plane vector loop demonstrates that but for the short arc of the septal vector, the balance of forces during ventricular accession results in an entirely right, posterior loop which is clockwise in direction. The initial portion of this vector loop projects positively on leads from the entire front and left lateral portions of the chest, producing a small r wave. The remainder of the loop projects negatively in these same areas, producing a deep S wave across the front and left lateral side of the chest. This is a rare variant of the vectorcardiogram seen in patients with right ventricular hypertrophy, which usually is found to be inscribed in the right lower, anterior octant. This unusual location of the horizontal plane vector could be the result of anatomical rotation of the heart posteriorly about its sagittal axis. The degree of rotation from the position occupied by most vector loops of patients with right ventricular hypertrophy to this one is only about 60 degrees. The relative position of the left and right ventricles as seen on angiocardiogram, however, did not appear grossly dissimilar to others with vector loops in the usual positions. It is possible, therefore, that this change was entirely the result of an unusual balance of forces which were the result of an unusual pattern of hypertrophy.

CASE 2.—The probable diagnosis of interatrial septal defect with marked pulmonary hypertension was made in V. D., a 32-year-old, white woman. Fluoroscopy revealed right ventricular hypertrophy, a large pulmonary artery, and dilated, pulsatile, intrapulmonic vascular markings. Cardiac catheterization established the presence of an interatrial communication and right ventricular systolic pressure of 90 mm. Hg. Angiocardiography confirmed the findings of a large right atrium and ventricle. The electrocardiogram seen in Fig. 3*A* shows that the main ventricular deflections in the three standard leads are directed downward. There is a wide, late R wave in Lead V_R; Leads V_F and V_L do not resemble any precordial leads. The unipolar chest leads show tall, notched R waves on the right side of the chest and equiphasic Rs or QRS complexes on the left. These are characteristic of right ventricular hypertrophy. The vectorcardiogram of this patient (Fig. 3*B*) shows that the major portion of the vector loop is found in the right upper, anterior octant. In the frontal plane, the pathway begins with a normally formed septal deflection which proceeds anteriorly and to the right. The vector axis then turns sharply to the left and downward for a short segment. This results in an R wave in Leads I, II, and III. A 180 degree turn is then made, and the centrifugal limb is directed sharply upward and to the right. This results in the writing of negative deflections in all three standard leads. After completing a figure 8, the loop returns to its starting point. In the horizontal plane, the vector loop is clockwise in rotation and directed laterally and to the right, as in most patients with marked right ventricular hypertrophy. This results in high R waves over the right precordium and deep S waves over the left.

The right superior, anterior position assumed by this vectorcardiogram adequately accounts for the bizarre axis deviation and predominantly negative deflections in the standard leads. Anatomical rotation of the heart, clockwise as seen by the observer, about its anteroposterior axis could conceivably produce this effect. The degree of rotation necessary from the position usually assumed by such cases (plus 140 degrees) is about 70 degrees of the arc. Angiocardiographic study did not show such a change, but since it is difficult to estimate position accurately, this does not constitute definitive and final negative evidence.

CASE 3.—A diagnosis of Eisenmenger's complex was considered most likely in the case of T. C., a 3-year-old, white male infant. Fluoroscopy revealed a normal-sized heart, prominent pulmonary artery, considerable pulsation of hilar vessels, and a moderate degree of right ventricular hypertrophy.

The electrocardiogram of this patient is seen in Fig. 4*A*. The major deflections are directed downward in all three standard leads, though Lead III has an R wave of some size. There is a tall, wide R wave in V_R. Lead V_L does not resemble any precordial lead, and V_F resembles Lead

V_6. This might be termed a semivertical heart. Unipolar chest leads are characteristic of right ventricular hypertrophy, as they show tall R waves on the right from V_{R7} to V_1 and small r, deep S waves in V_5 through V_9. The vectorcardiogram seen in Fig. 4*B* demonstrates that the spatial vector lies mainly in the right upper, anterior octant, thus producing predominantly negative deflections in the three standard leads. The frontal and horizontal plane loops proceed in a clockwise direction, characteristic of right ventricular hypertrophy patterns. The only

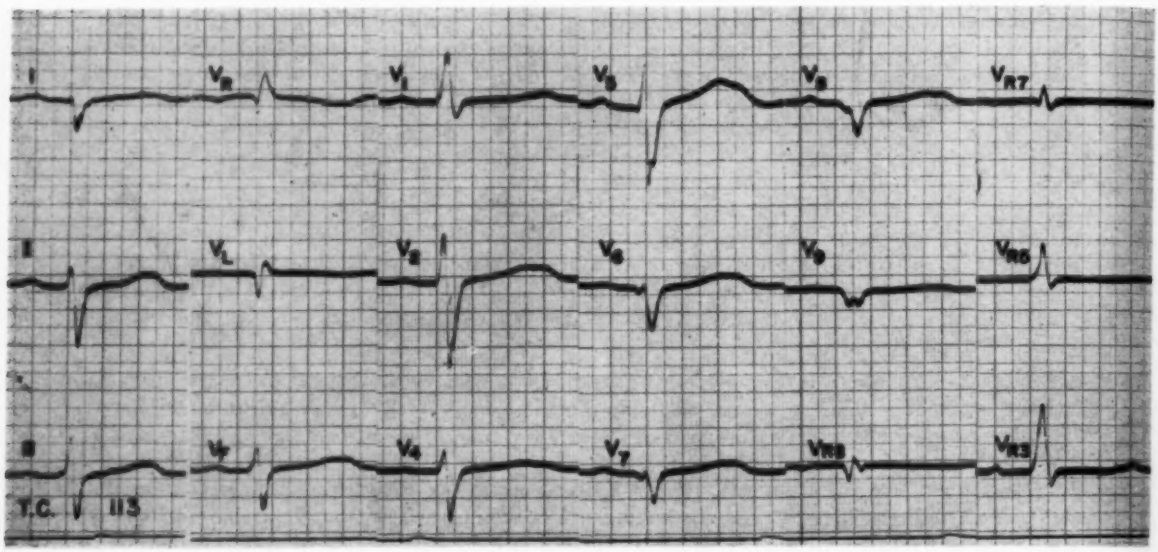

Fig. 4*A*.—Electrocardiogram of T. C. taken at quadruple speed, showing predominantly negative deflections in the standard leads and a typical pattern associated with right ventricular hypertrophy in precordial leads.

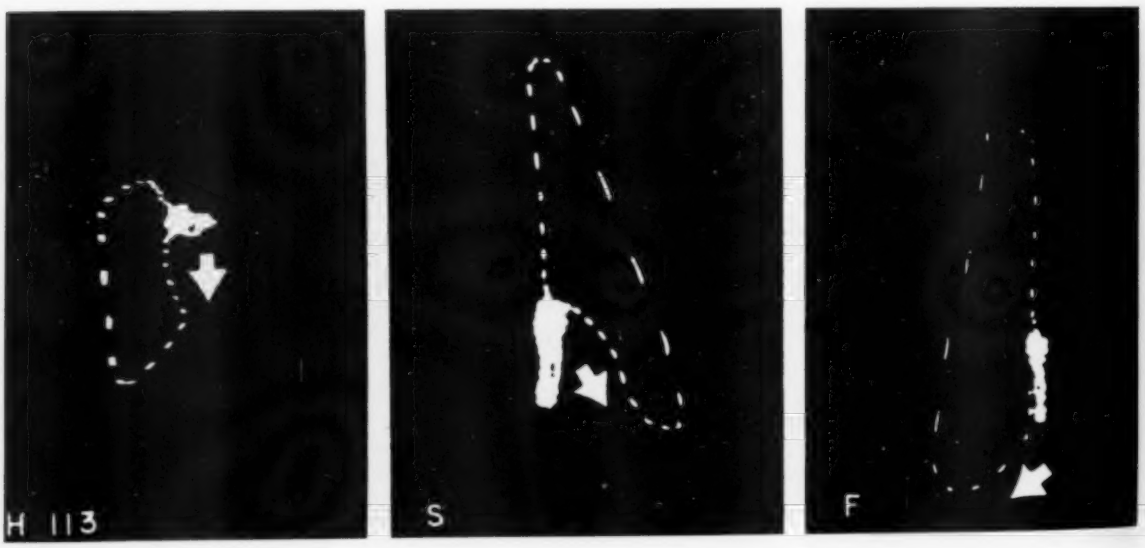

Fig. 4*B*.—Vectorcardiogram of T. C., showing clockwise rotation in frontal and horizontal planes and counterclockwise rotation in the sagittal plane. The initial one-half of the loop is inscribed in the right lower, anterior octant and the terminal one-half in the right upper, anterior octant.

difference between this vectorcardiogram and those customarily found in right ventricular hypertrophy is the markedly upward direction taken by this loop.

Anatomical rotation of about 120 degrees about the anteroposterior axis would be necessary in order to create a vector loop of this type from one located in the usual position occupied by those of patients with right ventricular hypertrophy of similar degree. There was no sign of such marked change. It is more likely that this, as in the previous case, was due to an unusual balance of forces.

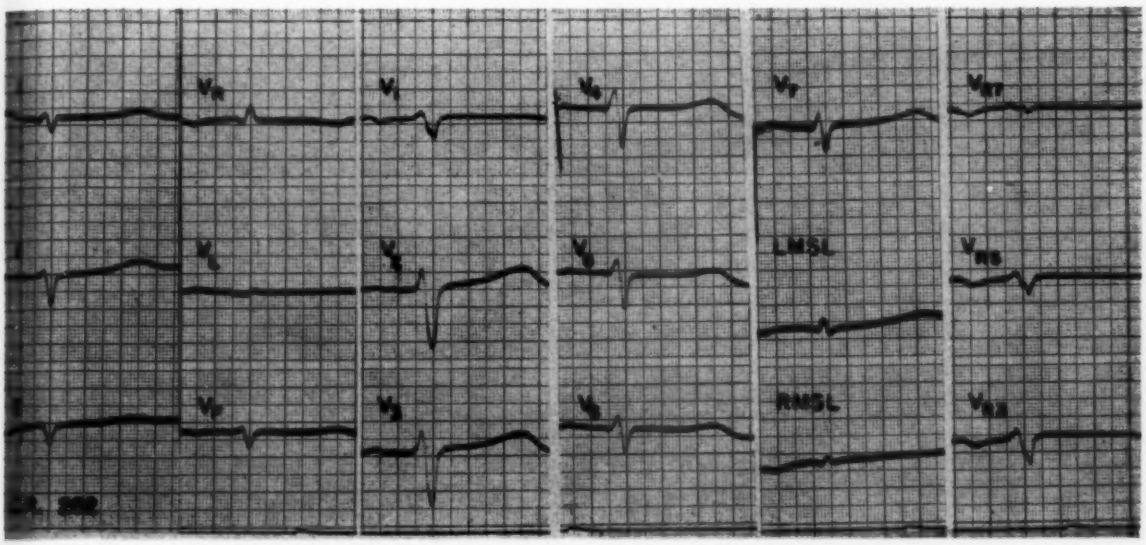

Fig. 5*A*.—Electrocardiogram of C. R. taken at quadruple speed, showing downwardly directed QRS deflections in the standard leads and a small r, deep S pattern from V_{R5} through V_7.

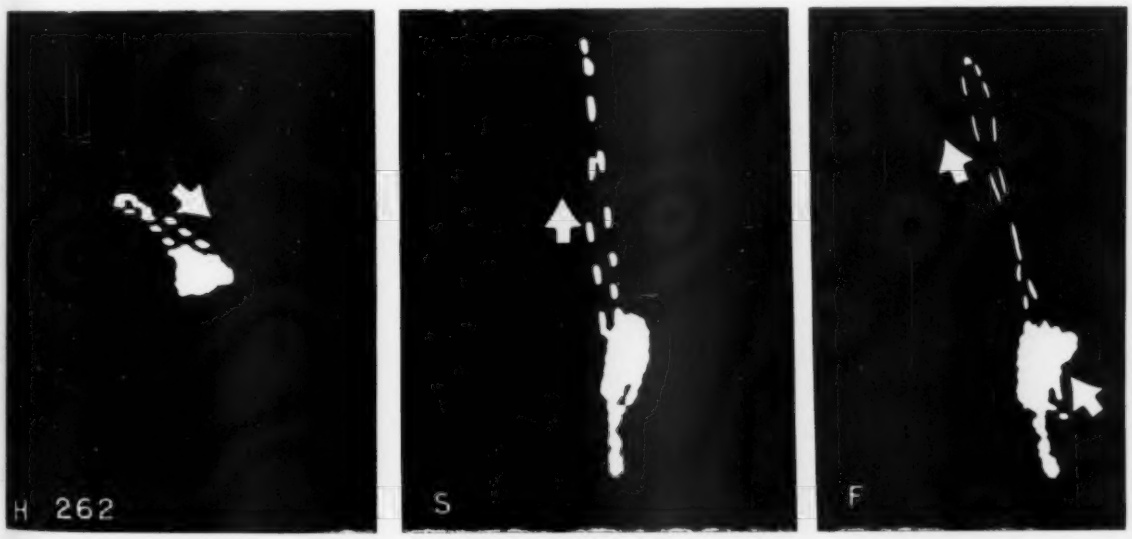

Fig. 5*B*.—Vectorcardiogram of C. R., showing a small initial segment of the loop which is directed downward and to the left, whereas the remainder of the loop is directed almost vertically upward and lies in the right upper, posterior octant.

CASE 4.—The diagnosis of isolated pulmonary stenosis was established by cardiac catheterization in C. R., a 14-year-old, white girl. The right ventricle was found to be enlarged upon fluoroscopic examination and by angiocardiography. Right ventricular systolic pressure was 70 mm. Hg. The electrocardiogram seen in Fig. 5*A* shows predominantly negative deflections in the three standard leads, a wide, tall R wave in Lead V_R, and small r, deep S waves from V_{R5} through V_7. This encompasses virtually two-thirds of the circumference of the chest. Positivity predominates only over the back in the left and right scapular leads.

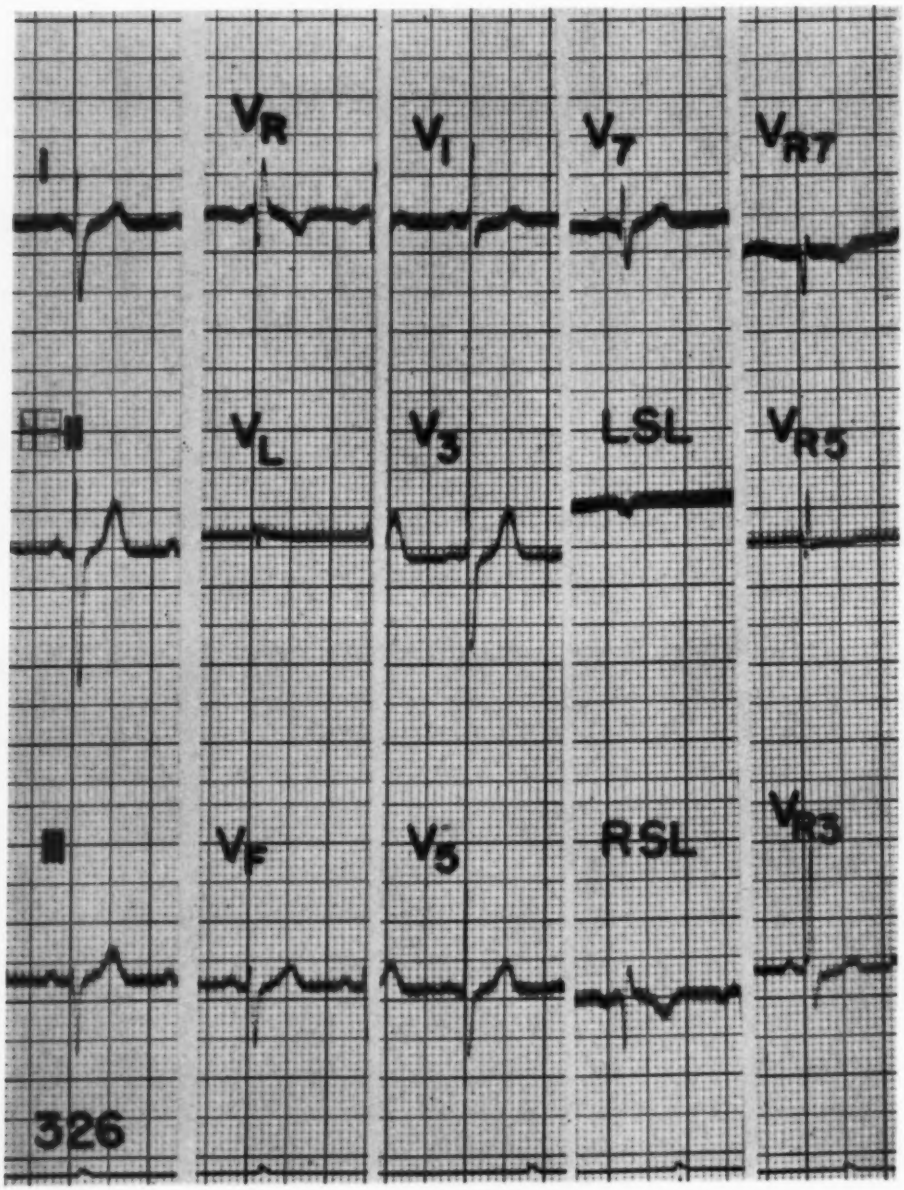

Fig. 6*A*.—Electrocardiogram of S. D. taken at the customary speed, showing negative deflections in the standard leads and a typical pattern of right ventricular hypertrophy in precordial leads.

The vectorcardiogram seen in Fig. 5*B* is most unusual in that the spatial vector loop is very narrow, resembling a hairpin. The loop lies mainly in the right upper, posterior octant. Thus, from the frontal plane projection, we can see that Lead I will be small and diphasic, but mainly negative, and Leads II and III will be markedly negative. A small initial part of the loop is obscured by the T wave. This is directed downward and slightly to the left and produces the small r waves in all three leads. The major part of this loop projects positively toward Lead V_R and is the cause of the tall R wave there. Since the horizontal plane vector loop is directed posteriorly, small r and deep S waves are observed across the anterior surface of the chest and around the left lateral side. The only positivity is posterior and is seen in leads from left and right scapulas. Such a bizarre direction would require impossible degrees of anatomical rotation were it due to this alone.

Observation of the angiocardiogram and fluoroscopic image revealed no unusual cardiac position whatever.

Again here, it is believed that the results were due to electrical rather than anatomical shifts of orientation.

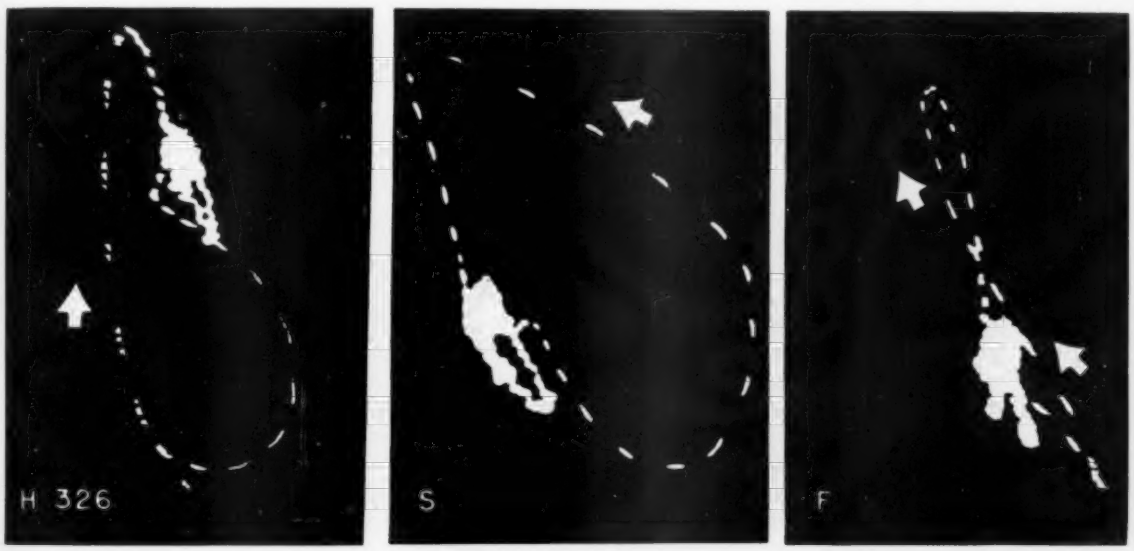

Fig. 6*B*.—Vectorcardiogram of S. D., showing an initial left lower, anterior orientation and a final right upper, posterior orientation.

CASE 5.—S. D., a 6-year-old, white female child, was diagnosed as having probably an isolated pulmonary stenosis, on the basis of the location and quality of the murmur heard, the absence of cyanosis, and the small, quiet pulmonary vascular markings seen fluoroscopically. The presence of right ventricular hypertrophy or enlargement was established by fluoroscopy. The electrocardiogram seen in Fig. 6*A* shows predominantly downward deflections in the standard leads. If the R wave in Lead I were a few millimeters taller, one would state that there was a tendency to left axis deviation.

The unipolar extremity leads show a tall, wide R wave in V_R. Leads V_L and V_F do not resemble any of the precordial leads. The unipolar chest leads show a pattern associated with right ventricular hypertrophy, consisting of a tall, notched R wave in Leads V_{R5} through V_1 and RS or rS complexes in V_5 and V_7. The vectorcardiogram, seen in Fig. 6*B*, is similar in form to that of Case 2, only that this vector loop is rotated some 50 degrees farther toward the left in clockwise direction (as seen by the observer) about the anteroposterior axis. In the frontal plane, the vector proceeds first downward and to the left, resulting in positive deflections being written in all three standard leads and Lead V_F. It then courses upward and slightly to the right,

resulting in deep negative deflections in the standard leads and V_F and positivity in V_R. The QRS complex in V_1 is small and diphasic because the vector runs almost perpendicular to its axis.

This vector was rotated approximately 120 degrees clockwise about the anteroposterior axis (as seen by the observer) from the mean position of the majority of vectorcardiograms seen in patients with right ventricular hypertrophy. There was no fluoroscopic evidence of such rotation. This case completes the group of those with predominantly negative deflections in the standard leads. They constitute a progressive series of vectorcardiograms, each of which is inscribed in a more superior position than the one preceding. The progression is in a clockwise direction. It is obvious that further shift of the vector in this clockwise fashion will produce positive deflections in Lead I and negative deflections in Leads II and III. Thus, left axis deviation will be produced. The cases to follow exhibit just such a progression. There is, therefore, no qualitative difference between bizarre axis and left axis deviation in patients with right ventricular hypertrophy.

2. Left Axis Deviation.—

CASE 1.—The diagnosis of an interatrial septal defect was made by angiocardiography in I. B., an 8-year-old girl. The heart was greatly enlarged and globular. The pulmonary artery was very prominent. The right atrium and ventricle were markedly enlarged.

The electrocardiogram, seen in Fig. 7*A*, shows a left axis deviation. Lead V_R is small and diphasic. Lead V_L resembles the complexes of the left side of the chest, and V_F resembles V_4. This would be called a semihorizontal heart. The unipolar chest leads show a small r, deep S wave from Lead V_{R_7} through V_2. Tall R waves are found across the left side of the chest. The vectorcardiogram, seen in Fig. 7*B*, is very unusual. In the frontal plane, the initial portion of the loop is directed downward and slightly to the right. Thus, positive deflections are found in Leads II and III. The loop then turns to the left and ascends into a left, superior quadrant, producing the negative deflections in Leads II, III, and V_F and the positivity in Lead I. The vector loop is oriented perpendicularly to Lead V_R and, hence, the diphasic nature of that lead. The horizontal plane vectorcardiogram is in the form of a figure 8 lying in the left, posterior quadrant. The loop begins anteriorly but then turns backward and to the left. This left posterior position results in negativity predominating on the right side of the chest and positivity on the left. It can be seen that clockwise rotation of some 30 degrees about the anteroposterior axis would produce the left axis deviation seen here from the concordant S deflections of the last case (5). By now, however, we are certainly entirely out of range of any simple anatomical rotation which could produce these changes from the ordinary vectorcardiogram of right ventricular hypertrophy.

CASE 2.—Isolated pulmonary stenosis was proved in L. C., a 17-year-old, white girl, by cardiac catheterization and angiocardiography. There was marked systolic hypertension in the right ventricle and a pronounced degree of pulmonary stenosis. Angiocardiograms revealed that the wall of the right ventricle was greatly thickened, but its size was not greatly increased.

The electrocardiogram of Fig. 8*A* shows left axis deviation and an M-shaped complex in Lead I. Lead V_R has a high R wave. Lead V_L resembles the complexes of V_1, and V_F those of V_3 and V_4. This would then be termed a semivertical heart. The unipolar chest leads reveal an RsR′ complex in V_{R_5} through V_1, seen most clearly at V_{R_3}. The vectorcardiogram seen in Fig. 8*B* is very similar to Case 4 of the concordant S group except that additional rotation of a mere 20 degrees clockwise about the anteroposterior axis suffices to create upright complexes in Lead I instead of negative ones and, therefore, a left axis deviation. The upright portion of the complexes of Leads II and III is a projection of the first segment of the vector which courses downward, as in all other cases reported. The horizontal plane vectorcardiogram is small and anterior. Why it is so small and yet reflects usual-sized complexes in the precordial leads is difficult to answer. The general configuration of the loop gives the explanation for the RsR′ complexes seen in V_{R_3} and V_1. The initial part of the loop, the resultant of septal forces, presumably, runs downward, anteriorly, and slightly to the right. This projects as positivity along the lines from the V_{R_3} or V_1 electrodes to the electrical center of the heart, and an R wave is written. The loop then turns to the left and reaches the null point of the plane of these electrodes, and this is seen as a deep notch extending down to the isoelectric line. The loop then turns sharply in a clockwise direction, and the centripetal limb returns anterior to the centrifugal limb. This

produces another rise in positive potential and the R_1 wave is written. Study of the RsR' complex has been presented elsewhere.[18] For reasons which cannot be expounded here, it is believed that this does not represent bundle branch block, but that it is a variant of the right ventricular hypertrophy pattern. It is not believed that this vertical vector could be due to anatomical rotation alone. Certainly neither angiocardiogram nor fluoroscopy revealed any changes of position. It is more likely that uncommon augmentations and opposition of electrical forces have produced this result.

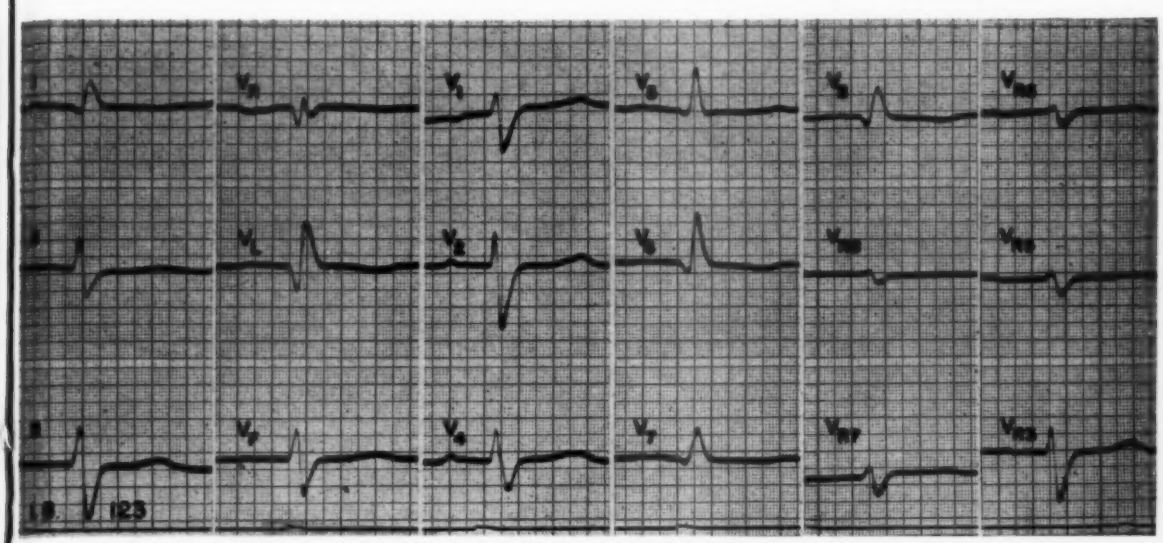

Fig. 7*A*.—Electrocardiogram of I. B. taken at quadruple speed, showing left axis deviation. In the precordial leads, small r, deep S complexes are seen in V_{R7} through V_2 and qR complexes in V_5 through V_8.

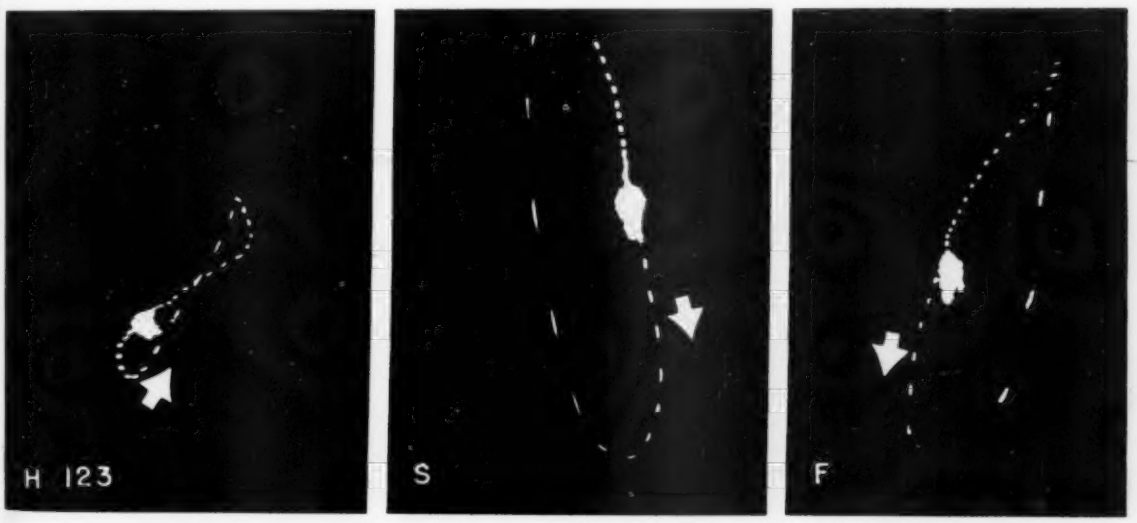

Fig. 7*B*.—Vectorcardiogram of I. B., showing an initial right lower, anterior orientation and a terminal inscription in the left upper, posterior octant.

CASE 3.—A diagnosis of interatrial septal defect was made in the case of C. M., a 23-year-old, white man. This was based upon the history of a murmur since 3 years of age, gracile habitus, absence of cyanosis or dyspnea, a marked precordial bulge, and the fluoroscopic findings of an enlarged heart, right ventricular enlargement, a prominent, pulsating pulmonary artery, and the very rapid dilution of dye in the right atrium during angiocardiography. The electrocardiogram seen in Fig. 9*A* shows left axis deviation in the standard leads, though a shallow, somewhat widened S_1 is present. There is a tall, wide R wave in Lead V_R. Lead V_F resembles V_1, and V_L does not

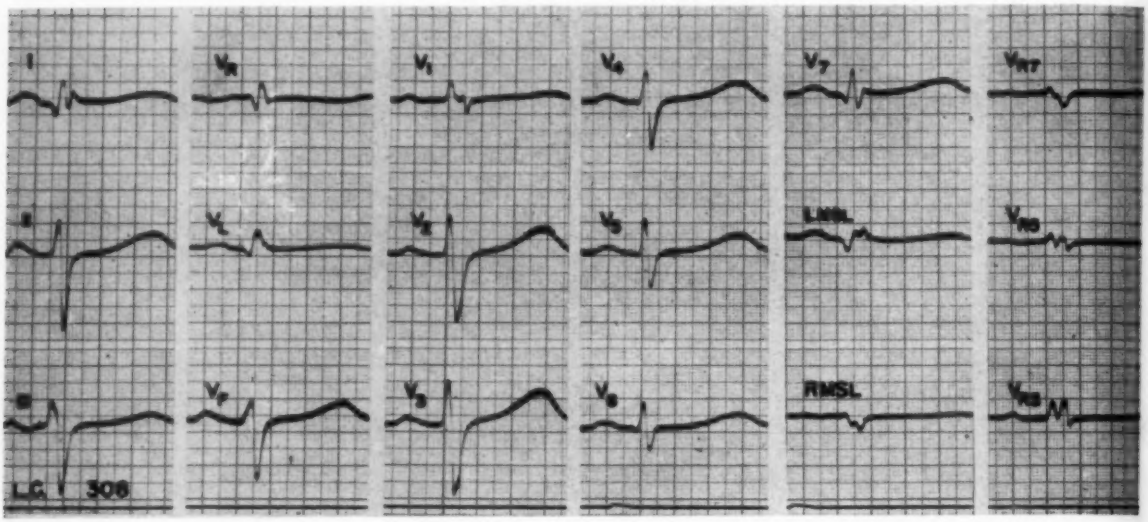

Fig. 8*A*.—Electrocardiogram of L. C. taken at quadruple speed, showing a left axis deviation and an RSR′ complex in precordial leads V_{R5} through V_1.

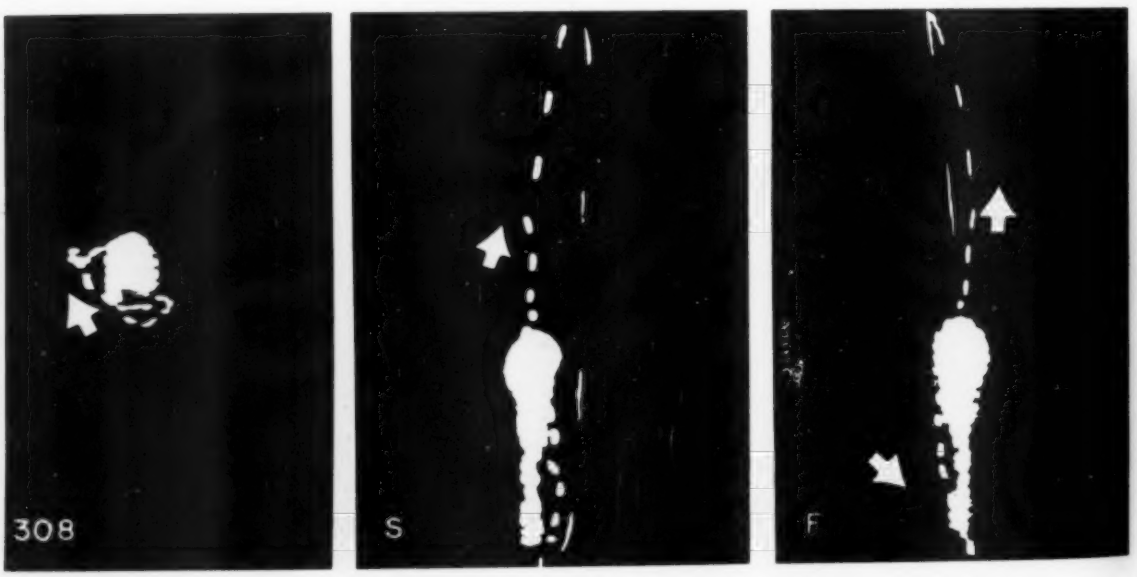

Fig. 8*B*.—Vectorcardiogram of L. C., showing the vector loop to be directed to the right and anteriorly, then to the left and downward, and then to the left and vertically upward.

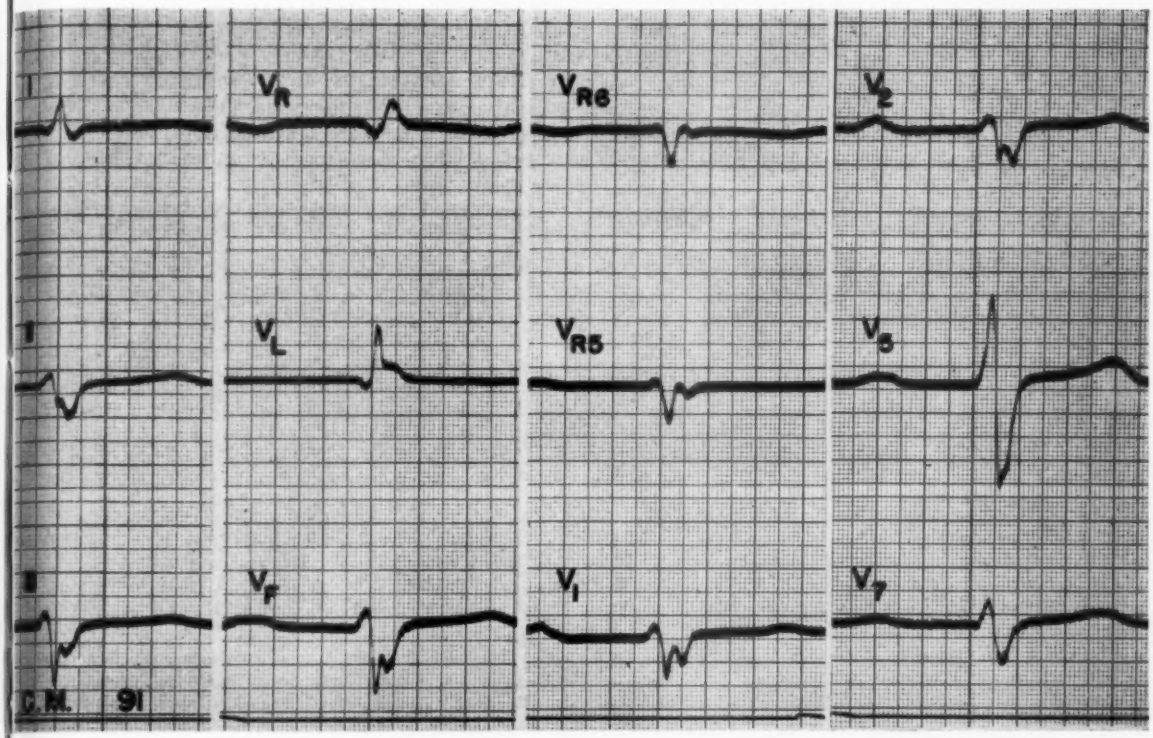

Fig. 9*A*.—Electrocardiogram of C. M. taken at quadruple speed, showing left axis deviation and an equiphasic, W-shaped complex in V_{R5} through V_2.

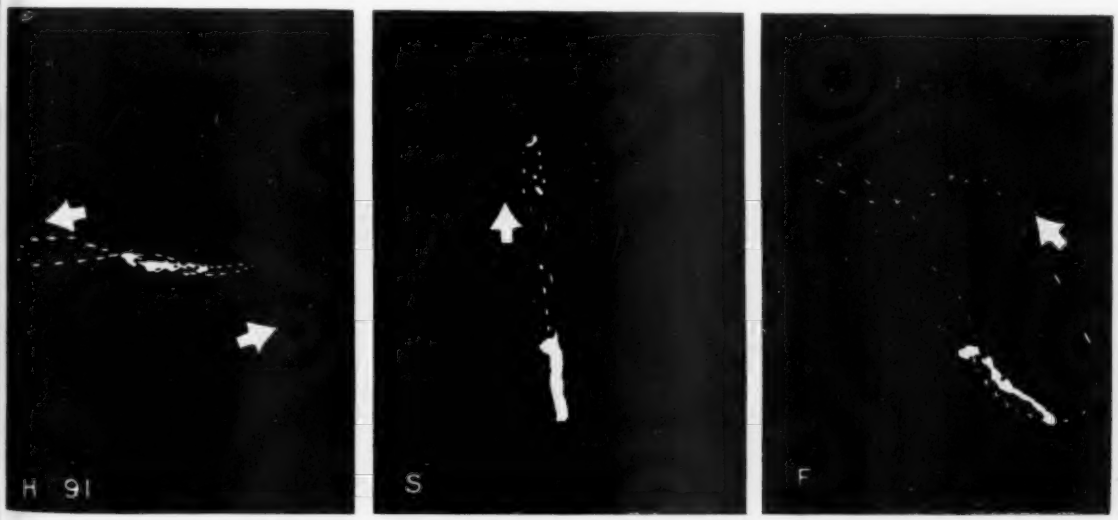

Fig. 9*B*.—Vectorcardiogram of C. M., showing the predominantly left, upper quadrant orientation.

resemble any precordial lead. This might be termed a semihorizontal heart. The precordial leads of the right side of the chest consist of a small r and widened, notched S wave. Those of the left side consist of an equiphasic RS complex.

The vectorcardiogram, seen in Fig.9*B*, was inscribed chiefly in the left upper quadrant lying neither anterior nor posterior, but centrally located as seen in the horizontal plane. Rotation in the frontal plane is counterclockwise. The horizontal plane vectorcardiogram reveals the nature of the bizarre precordial pattern. The centrifugal limb runs anteriorly and to the left,

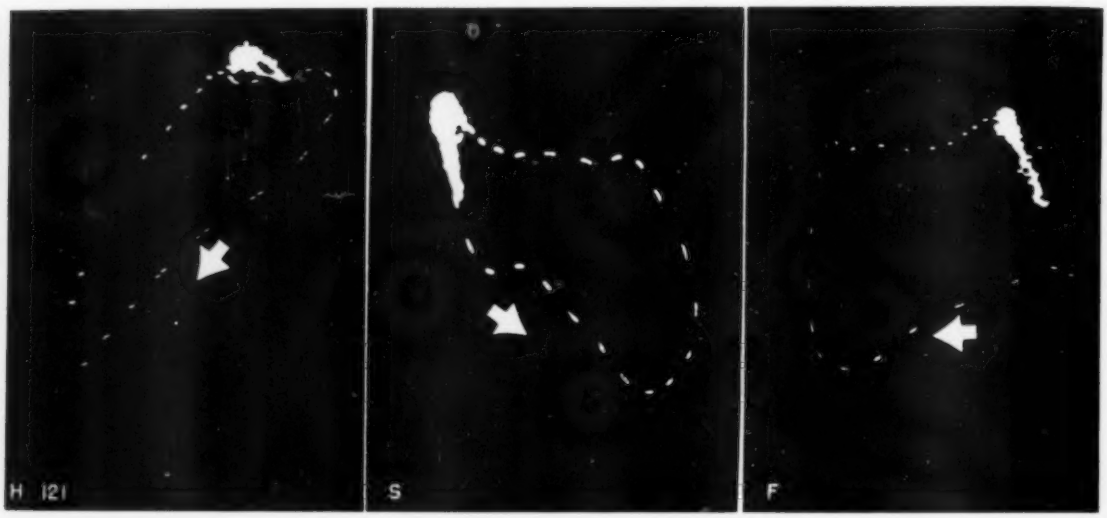

Fig. 10*A*.—Vectorcardiogram obtained in a patient with tetralogy of Fallot, showing the characteristic features of an orientation in the right lower, anterior octant and clockwise rotation in frontal and horizontal plane projections of the QRS SÊ loop.

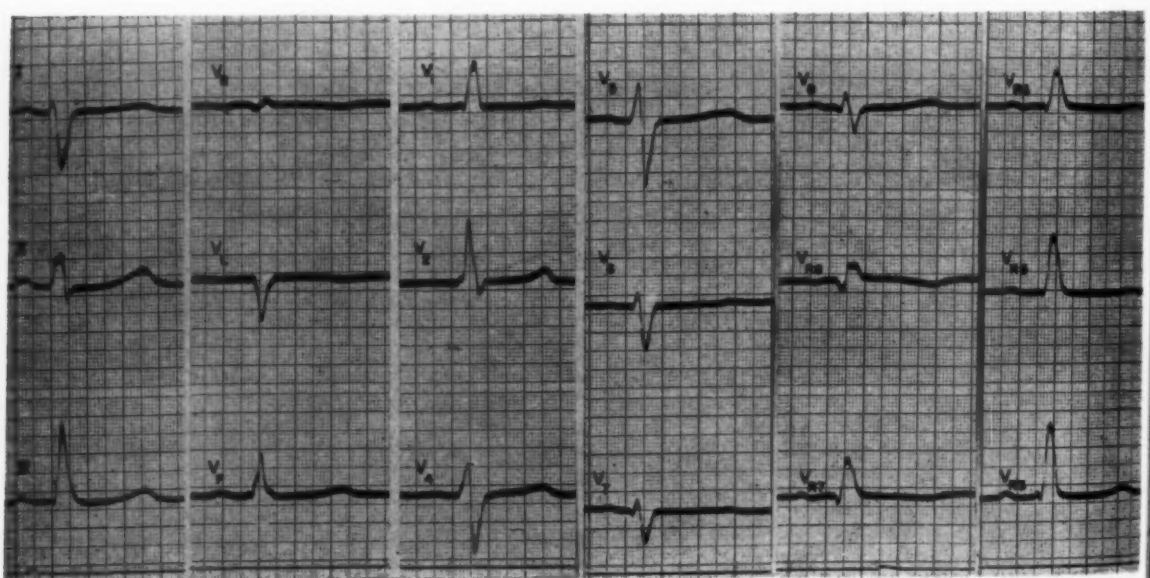

Fig. 10*B*.—Electrocardiogram showing marked right axis deviation, tall, notched R waves in Leads V_{R5} through V_1, and small r, deep S wave in Leads V_2 through V_7.

producing a small r wave at V_1 and tall R at V_7. It then turns counterclockwise and runs slightly posterior to, but parallel with, the outgoing limb. This then crosses over to the right side, loops in a figure 8, and returns to isoelectricity. The part of the vector loop which lies on the right side produces negative deflections in V_7 and positive ones in V_1. Due to the figure 8 form, the S wave in V_7 is notched and slurred.

Comments upon this vectorcardiogram are the same as those made upon the other two of this group.

Included for comparison is Fig. 10*A*, a typical vectorcardiogram, which was obtained in a patient with a tetralogy of Fallot. It lies in the right lower, anterior octant. Therefore, positivity is evidenced in standard leads II and III, V_F, and V_R; negativity is seen in standard lead I and V_L. The chest lead electrocardiogram, as reasoned from the horizontal plane vectorcardiogram, should and does show tall R waves which are notched on the upstroke in right-sided leads and small q, small r, deep S waves in left-sided leads. The electrocardiogram in Fig. 10*B* does show just these features.

DISCUSSION

Two explanations of the origin of these electrocardiograms have been advanced. One explanation states that the enlarging right atrium and ventricle have caused an unusual degree of anatomical rotation of the heart.[11,16] The apex of the heart is believed to be displaced posteriorly, and it is postulated that the heart is in a markedly vertical position and is rotated clockwise about its longitudinal axes. A second explanation given is that concomitant left ventricular hypertrophy is present.[7,13]

The first, or rotational, theory derives from a comparison of the unipolar extremity leads and their resemblance to certain precordial leads. It rests upon the belief that ventricular complexes of arbitrarily assigned form which are supposed to represent the "back of the heart," "ventricular cavity," "right ventricular surface," "left ventricular surface" are projected on to the right or left shoulders or registered by the left leg electrode. The exact rotation of the heart and its anatomical position are then determined by addition of these abovementioned complexes until a result is obtained which accords with the electrocardiogram. This rather circular reasoning is not entirely adequate. There is no good evidence that these areas are true entities which can produce a uniform and predictable ventricular complex over their entire extent. There is some evidence that this is not so.[17] Moreover, very frequently, the unipolar extremity leads do not resemble any of the precordial leads. This is not unexpected in as much as the former are derivatives mainly of the frontal plane projection of the heart vector, and the chest leads are derived chiefly from the horizontal plane projection. Analysis of the eight cases reported here reveals that the position of the heart was indeterminate in four, semihorizontal in two, and semivertical in two. Thus, little information is gained from this.

The second, or biventricular hypertrophy, theory is untenable in view of the results from an excellent series of patients with the concordant S-type electrocardiograms, all of whom had right ventricular hypertrophy at autopsy. Even more convincing is a reported case of this series who developed an S_1, S_2, S_3 type of electrocardiogram during the progress of increasing right-sided congestive failure secondary to pulmonary tuberculosis.[12]

Similarly, in this study the electrocardiograms presented have all been obtained in patients with well-authenticated right ventricular hypertrophy. There were three patients with interatrial septal defects, one with Eisenmenger's complex, three with isolated pulmonary stenosis, and one with a tetralogy of Fallot. Problems, therefore, of complicating biventricular hypertrophy are not present. We must therefore assume that the form and pattern of the ventricular complexes, however bizarre, are in some manner determined by the increased thickness of the right ventricular wall or the increased mass and surface area of the right ventricle. It does not appear likely that anatomical rotation of the heart alone would be capable of causing such marked alterations in the position and form of the vectorcardiogram as are observed here. There is no evidence in the vectorcardiogram of any abnormality of the conduction system or change in the time relationships of the wave of accession. There is, however, not enough experience with this to make any definite statements other than that the usual features of bundle branch block are not present. These vectorcardiograms differ markedly in form and rotation from those obtained in patients with hypertrophy of the left ventricle.

SUMMARY AND CONCLUSIONS

Vectorcardiograms of an unusual type which were obtained in patients with congenital heart disease associated with well-authenticated hypertrophy of the right ventricle have been described. These were vectorcardiograms of patients whose electrocardiograms showed an unusual axis deviation or left axis deviation.

1. The vector loops could be arranged into a graded series, progressing from the customary right axis deviation through those with negative deflections in all three standard leads to those with frank left axis deviation. It was found that the vector loops of the above were inscribed in the right lower quadrant, right upper quadrant, and left upper quadrant, respectively, as shown in the frontal plane projection.

2. The unipolar chest lead electrocardiogram corresponded closely to the horizontal plane projection of the QRS SÊ vector loop, and accurate prediction of chest lead patterns could be made from it. Chest lead patterns were of four types.

A. The first pattern consisted of tall R waves or an RSR′ complex obtained in leads from the right side of the chest. There were four such cases. The QRS SÊ loop was found to be inscribed in the right *anterior* quadrant in all four.

B. Two patients showed a second pattern which consisted of small r waves and deep S waves across the entire front of the chest. In these, the QRS SÊ loop was found to lie in a right *posterior* quadrant.

C. In one patient, a third pattern was seen. Small r, deep S waves were obtained in leads from the right precordium, and tall R waves were found only in leads from the left side of the chest. The vectorcardiogram was inscribed in the left posterior quadrant.

D. Finally, in one patient, equiphasic RS complexes were recorded circumferentially about the chest. The vectorcardiogram was found to

lie directly in the sagittal plane of the body and to be distributed equally to the left and the right.

3. Careful examination of angiocardiograms and careful fluoroscopy failed to disclose any anatomical rotation or displacement of the heart of sufficient degree to account for the very markedly unusual vector pathways reported here. The position of the heart in the thorax of these patients was indistinguishable from the position in any other patient with a similar diagnosis and similar heart size. We do not believe that anatomical rotation plays an important role in the production of these bizarre and paradoxical electrocardiograms. We believe that the vectorcardiograms seen in patients with right ventricular hypertrophy are the result of the increased thickness of the wall and increased mass and surface area of the right ventricle which in some way alters the balance of the electromotive forces of accession. The unusual vectorcardiograms reported here are similarly the result of the individual patterns of hypertrophy and balance of forces.

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Review of Recent Advances

A CONSIDERATION OF THE MECHANISM OF CONGESTIVE HEART FAILURE

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IT IS generally accepted today that the mechanism of congestive heart failure is not clearly understood,[1-7] although it had previously been considered by most physiologists and clinicians to have been settled. There were some, the minority surely, who never accepted the explanations current at the time.[8] Several years ago some investigators revealed the inadequacy of the data available to support the accepted concepts. As a result, the problem was carefully reconsidered, and vast deficiencies in knowledge concerning the mechanism of congestive heart failure were revealed. This has led to considerable discussion and experimentation, particularly regarding disturbances in physiology, some of which has been fruitful, though congestive heart failure still remains one of the important unsolved problems in medicine.

The complexity of the problem and inability to produce the syndrome in experimental animals have been responsible for errors in research and thought as well as for slow progress. Most errors have occurred because of variations in the clinical state of the failure when studied, inadequacies of the methods employed, complicating clinical states, complicating influences of associated therapeutic procedures, or because the sequelae of failure of the heart were being observed rather than actual failure of the pump itself. These and other factors have created difficulties in the integration and comparison of observations, leading to considerable misunderstanding and confusion. In part because of these factors, no major advance has been made toward the solution of this problem.

This paper is intended to present the problem of congestive heart failure as seen by us, in an attempt to clarify certain aspects and in order to point out certain established facts and inconsistencies in interpretation. It should be reiterated that details of the mechanism or mechanisms of congestive heart failure remain unknown. Several aspects of them will be indicated. The numerous gaps in current knowledge will become evident from this discussion. Obviously, most of these concepts and data are not new, but it is likely that some of them have not been considered generally in this fashion. Although Starling clearly presented the problem over fifty years ago,[9] little additional information of a

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fundamental nature has since been added. About ten years ago Starr and Rawson[4] again lucidly presented certain basic aspects of the hemodynamic principles concerned with congestive heart failure. These have been disregarded or forgotten by many. The concepts previously described by these investigators, as well as by others, will be reviewed in this presentation.

DEFINITION OF CLASSICAL CONCEPTS

Failure to define properly the clinical syndrome under study has caused confusion and errors in interpretation of data. In this discussion, except when otherwise specifically stated, *chronic congestive heart failure* is the clinical syndrome under consideration. This syndrome, when fully developed and not receding, is characterized essentially by dyspnea, generalized edema, which is most severe in the most dependent portions of the body, generalized and symmetric venous hypertension, diffuse hepatomegaly, and possibly peritoneal or pleural transudates or both. Bilateral basal râles in the lungs, accentuated pulmonic second sound, pulsus alternans, gallop rhythm, orthopnea, weakness, and many other manifestations may be present. The finer details of the clinical syndrome, which are well known to most clinicians, are available in the literature.[10,11,12] Furthermore, attempts at a detailed description of the syndrome may actually divert attention from the fundamental physiologic processes.

The clinical manifestations observed at the bedside are mainly sequelae of cardiac disease or failure of the pump. Most observers investigating congestive heart failure have studied these sequelae rather than the heart or pump itself. This is understandable, since the pump cannot readily be studied, whereas some aspects of the sequelae are more easily approached.

For purposes of orientation, the two classical concepts of congestive heart failure are briefly defined.

1. *The Backward Failure Concept*[10,11,12].—With failure of a ventricle to pump adequately, the blood returning to it accumulates proximally in the atrium and veins. In association with this accumulation of blood in the veins, venous pressure increases, the venous blood pressure gradient falls, venous stasis occurs, and blood accumulates under increased pressure in the small peripheral vessels. The increase in hydrostatic pressure produces a greater loss of fluid and electrolytes into the tissue spaces, resulting in formation of edema. Furthermore, with stasis there is anoxia of the capillary endothelium with resultant increased capillary permeability, which tends to enhance formation of edema (Fig. 1). When the capillaries near the peritoneal and pleural surfaces are sufficiently involved, transudation develops and ascitic and pleural fluids accumulate. Engorgement of the hepatic veins and sinusoids associated with increased intravascular pressure causes diffuse distention of the liver. Changes in renal function and in the urine are considered to be secondary to the venous hypertension and venous stasis with resultant impairment of renal blood flow, but until recently no role was attributed to the kidneys in the development of the syndrome of congestive failure.

2. *The Forward Failure Concept*[1,10,11,12].—With failure of the heart to pump blood forward the tissues of the body are deprived of a sufficient quantity

of blood, anoxia or asphyxia develops, the capillary endothelium increases in permeability, the oncotic and hydrostatic forces become unbalanced, edema develops, and the syndrome is established. There is stasis of blood in the peripheral vessels due to insufficiency of the heart. This increases the anoxia and produces cyanosis. Changes in renal function and urinary constituents are considered to be the result of impaired circulation through the kidneys (Fig. 2), but, again, until recently no one attributed any significant role to the kidneys in the development of the clinical syndrome.

CARDIAC EDEMA

In chronic congestive heart failure the fluid compartments of the body are increased, especially the intercellular fluid, including plasma volume. The interstitial fluid is *isotonic*; it has a *pH* of about 7.4 and has essentially the same

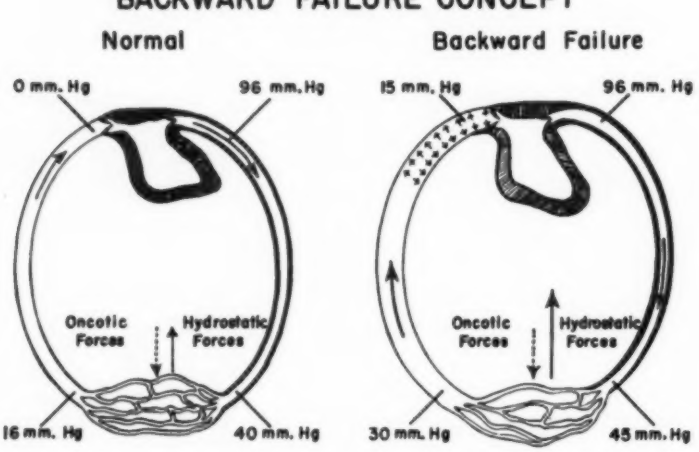

Fig. 1.—Diagrammatic representation of the classical concept of backward failure. The normal circulatory circuit is shown with normal mean pressures in the circuit and vectors of essentially equal magnitude indicating mean net effective oncotic and hydrostatic forces in the capillary bed. In the circulatory circuit with "backward failure" or congestion of blood proximal to the heart, there is an elevation in pressure in the venous system and a resultant increase in magnitude of the hydrostatic force, which tends to remove fluid from the vascular system at a greater rate than oncotic force which returns the fluid to the circulation. Because of this, edema develops.

electrolyte content as normal interstitial fluid. The protein content is approximately 0.5 Gm. per 100 c.c. Although these values are not considered to be significantly different from normal intercellular fluid, it is unlikely that unaltered normal interstitial body fluid has ever been collected in sufficient quantities to be studied. The various methods employed to collect interstitial fluid probably injure cells, blood vessels, and lymphatic vessels sufficiently to cause an abnormal type of fluid to accumulate. The fluid collected must be an exudate caused by trauma or a foreign body. Theoretic or indirect calculations of the chemical and physical characteristics of normal interstitial fluid are subject to well-known errors and are often based upon grossly erroneous assumptions. It is important to realize that the constitutional relationships of edema fluid to normal inter-

stitial fluid are not known precisely, and, therefore, any arguments concerning the mechanism of congestive heart failure which are based upon analysis of interstitial fluid must be regarded with skepticism.

OBSERVATIONS INCOMPATIBLE WITH THE CLASSICAL CONCEPTS

There are certain observations which are difficult to accept in terms of the classical concepts of the mechanisms of congestive heart failure. Only a few will be mentioned, since it is not possible to discuss all of them in a presentation such as this. Most of these are incompatible with the backward failure concept, once most generally accepted to explain the syndrome observed in congestive heart failure.

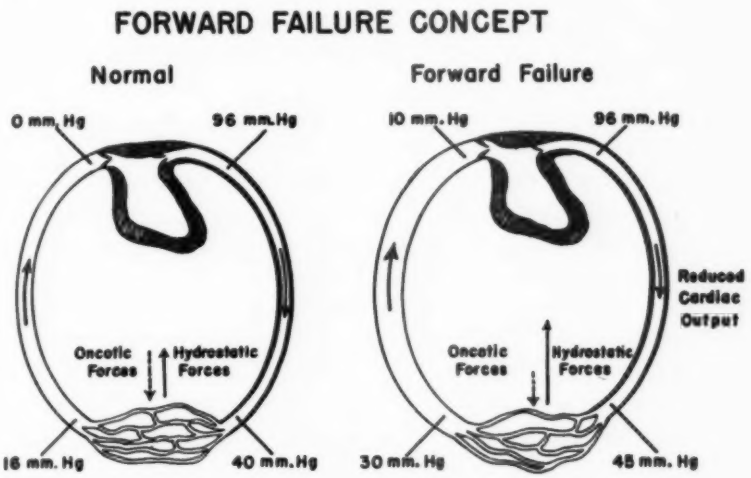

Fig. 2.—Diagrammatic representation of the classical concept of forward failure. The normal circulatory circuit is compared with that of forward failure. In the latter, insufficient blood is forced to the tissues. This is said to result in anoxia and an increase in capillary permeability to blood proteins which escape into the tissue spaces. This reduces the effective oncotic pressure which returns fluid to the blood vessels. Stasis of blood also occurs in the capillaries, venules, and veins because of loss of vis a tergo and failure of the failing heart to pump blood onward. Venous pressure is elevated, increasing hydrostatic forces in the capillaries. This produces further loss of fluid into the tissue spaces.

1. Although an increase in venous pressure probably contributes to the clinical picture, the edema and syndrome of congestive heart failure are not likely to be due to this alone, for clinical states with *venous hypertension* are known to exist with little or no clinical evidence of edema. For example, following ligation of the inferior vena cava for therapeutic reasons, pressure in the veins of the feet, with these parts at the level of the heart, has been observed to exceed 600 mm. of water without any appreciable clinical evidence of edema.[13,14] Edema of the feet is not more apt to develop in the feet of a tall man than in those of a short man when standing. Patients with cardiac tamponade from concretio cordis have been known to have generalized venous hypertension for many months without edema or the syndrome of congestive heart failure. Yet with continuation of the tamponade, something does occur in such a patient to produce the typical clinical syndrome. Factors such as infection and exertion[15] are likely

to precipitate the syndrome. Apparently some sequence of physiologic events must supervene before the picture of heart failure develops.

2. Although the *pressure in the capillaries* of the feet of a tall man standing exceeds the pressure in the arteries of his arms, edema of the feet does not ordinarily develop. It is unlikely, therefore, that the slight rise in capillary hydrostatic pressure associated with congestive heart failure could be completely responsible for the edema and the syndrome when even extreme elevations in capillary pressure of the feet are not associated with detectable edema there.

3. Many severe chronic *anoxic states* are known to exist in the absence of edema or the clinical syndrome of congestive heart failure. For example, high altitudes, congenital cardiac defects with right-to-left shunts, and chronic pulmonary disease are among the well-known clinical factors accompanied by generalized anoxia of the tissues in which the syndrome of congestive failure does not develop because of the oxygen deficiency alone. It is, therefore, unlikely that asphyxia or anoxia of the cells of the body generally or of any in particular is solely responsible for this syndrome. Patients sometimes have severe cyanosis in association with congenital cardiac disease, such as the tetralogy of Fallot, and yet live for many months or years before the pattern of heart failure develops. Just what mechanism is set into motion, how and where it is initiated, and details of the chain of physiologic events which follow the trigger mechanism that initiates the syndrome remain unknown.

4. A decrease in *cardiac output* has been agreed upon by most observers as the one necessary and truly primary physiologic phenomenon concerned with production of this clinical syndrome. The data on cardiac output obtained by various investigators in the presence of the syndrome have varied considerably. The cardiac output has been found to be normal, reduced, or elevated.[16-20] Although the investigations have been accepted as satisfactory, there have been obvious causes for differences in results. First, the methods employed for measurement of cardiac output are subject to error. The exact degree of accuracy has never been adequately determined for an intact man in congestive heart failure. A statistical evaluation would require a great number of experiments, and even then it is doubtful that the answer would be obtained. Furthermore, investigators have employed different methods for measuring cardiac output and attempts to compare these data have therefore been rather unsatisfactory.

Another cause for differences in interpretations of data among investigators is failure to define or even to recognize precisely the phase or state of the failure during the measurement of cardiac output. Two patients who are waterlogged and have clinical evidence of severe congestive heart failure may appear to be in the same state of failure; yet in one the disease may be progressively growing worse whereas in the other it may be stationary or improving. Only with careful clinical study may relatively gross differences among patients be discovered, and it may be that our present facilities do not even permit detection of significant differences. Furthermore, it is not known what constitutes a significant difference. In many instances the patients studied have received therapy of varying types, such as morphine, oxygen, bed rest, sedatives, or other agents which are known to influence the clinical syndrome. For an investigator to state that his

patient had received no therapy because digitalis or a mercurial diuretic had not been administered is only to oversimplify a complex problem.

Although an increase in cardiac output would be expected to be associated with or to precede improvement, this has not actually been observed in all instances.[16,20] Venesection has been reported to decrease cardiac output and still result in improvement of the patient.[16] The mechanism and significance of these observations have not been completely evaluated, regardless of the point of view entertained.

To explain the discrepancies in patients in failure with high cardiac output there have been introduced the concepts of "high" and "low" output failure. Certain clinical states, such as severe anemia and thyrotoxicosis, are known to be associated with higher cardiac output than certain other cardiac diseases studied under apparently identical circumstances. It is, therefore, considered that the resting output may be higher in patients with thyrotoxic or anemic heart disease and congestive heart failure than in a patient with arteriosclerotic heart disease and an apparently comparable state of failure, though both groups of patients are considered to have an insufficient output for the requirements of the tissues. This seems logical and may account for differences reported among investigators studying the problem, but some caution in accepting this concept completely is advisable, in view of the complexity of the problem of chronic congestive heart failure. For the present, therefore, cautious acceptance of high and low output failure concepts may be advisable because of its usefulness in thought.

Another aspect of cardiac output which has been offering difficulty is concerned with its relationship to venous pressure. Investigators continue to test the validity of Starling's law of the heart by employing measurements of pressure obtained in the right atrium or large veins as an index of ventricular filling. This is, of course, erroneous, since the venous pressure or intra-atrial pressure is not necessarily an index of the degree of ventricular filling or presystolic lengthening of the ventricular muscle fibers. Testing the correlation of the magnitude of cardiac output with these pressures can serve little useful purpose as an evaluation of Starling's law and its relationship to the concept of backward failure. It is not surprising, therefore, that many observers have been able to find no relationship between cardiac output and these pressures or the clinical syndrome of congestive heart failure. This is probably related in large measure to lack of relationship between maximum diastolic ventricular volume and venous pressure, the type and circumstances of the methods of study, state of the failure, preexisting therapy, and other variables difficult or impossible to evaluate. Furthermore, cardiac output and venous pressure would not even be expected to be correlated invariably anyway.

Cardiac output and function observed with the subject at rest in bed are not necessarily an index of the situation during exertion.[21] To use the former as a basis for speculation on the latter may lead to serious error. Observations during exertion in subjects with developing or progressive failure are particularly lacking. Furthermore, the forcing of fluids and electrolytes in patients in bed with impaired cardiac function in order to "produce" failure may also introduce error. This may be satisfactory for studying certain aspects of water and elec-

trolyte equilibrium or renal function during a positive balance of water and electrolytes, but it does not necessarily represent progressive failure insofar as the heart as a pump is concerned. The rate of intake of water and electrolytes will mainly influence the rate with which the clinical syndrome, especially the edema, will develop.

The foregoing comments are presented to illustrate further the complexity of the problem. It is evident that data concerning cardiac output must be studied carefully before being accepted or related to congestive failure. It will also become obvious that the crucial changes in cardiac output which initiate the clinical syndrome of congestive heart failure may exist for only a few beats of the heart or for too short a time to permit its observation by methods presently available.

5. Since the *protein content* of cardiac edema fluid is not considered to be greater than that of normal interstitial fluid, an increase in capillary permeability is not likely to be significantly concerned with the edema of congestive heart failure. However, the entire subject of capillary permeability is little understood. Furthermore, capillaries are freely permeable to water and electrolytes. Diffusion studies with radiosodium and radiochlorine in normal man and in patients with chronic congestive heart failure failed to show differences which could be attributed to variations in capillary permeability.[22,23,24] Variations in permeability were not definitely excluded by these studies, but it is extremely unlikely that capillary permeability is concerned with the development of the edema of congestive heart failure. Other mechanisms must be responsible for the syndrome.[18]

6. It has not been possible to produce the clinical syndrome of congestive heart failure in experimental animals even when practically all of the right *ventricular musculature* has been destroyed.[25,26] Certainly, however, it seems reasonable to suppose that this ventricle must fail to pump blood onward as efficiently as normally. According to the backward failure concept, blood should dam behind this ventricle. This does not happen, however, even following extensive or almost complete destruction of the musculature of the right ventricle. Therefore, either the concept of backward failure is erroneous or right ventricular musculature is not necessary to overcome resistance to blood flow in the pulmonary circuit. It is more likely that the former concept as presented is incorrect. However, it must be remembered that even if all the right ventricular musculature is destroyed, the pressure within the right ventricular cavity may be raised by the contracting contiguous left ventricle.[25]

7. Certain procedures, such as *low-salt diet* or administration of *mercurial diuretics*, are known to have beneficial influences upon the clinical syndrome, including disappearance of edema, decline in venous pressure, and reduction in size of the liver, without having any known direct effect upon the heart.[3,27] It is difficult to understand the mechanism by which a low-sodium diet acts beneficially on chronic congestive heart failure in terms of the "dam in the stream" concept of backward failure. Mercurial diuretics act primarily upon the kidneys without having any known significant effect upon the heart, yet the clinical syndrome improves with their administration. It is difficult to comprehend how

diuretics would be helpful if chronic congestive heart failure were merely a disturbance in hemodynamics, as presented by the backward failure or the forward failure concept.

8. A syndrome with manifestations similar to those of chronic congestive heart failure can be produced by excessive administration of *desoxycorticosterone acetate* (DCA), which is not supposed to have any significant direct cardiac action. This point in the argument must be considered cautiously because large doses of DCA have been shown to produce histologic changes in the myocardium. Furthermore, administration of large quantities of sodium and water will tend to produce or aggravate the syndrome in a patient with "poor cardiac reserve." These procedures act upon extracardiac mechanisms and apparently contribute to the clinical pattern referred to as the sequelae of failure of the heart as a pump.

Administration of large amounts of water and electrolytes to patients with anuria or oliguria due to renal disease will produce a similar syndrome. This, however, *by definition* is not congestive heart failure.

It is evident from the foregoing discussions that the clinical pattern of chronic congestive heart failure or passive congestion cannot develop from merely a "dam in the stream." To consider this statement more carefully, it is essential that the hemodynamic principles presented to explain the concepts of backward and forward failure be re-examined in some detail to search for possible errors.

TWO CONCEPTS OF DEFINITION

Prior to a discussion of hemodynamics, it should be pointed out that:

1. When congestive heart failure is designated as the syndrome under consideration, it is, by definition, necessary that the heart be involved in its mechanism. The identical clinical syndrome may be encountered in other disease states, but these symptoms and signs are not *pathognomonic* of heart failure. It is likely that the syndrome of anasarca, venous hypertension, hepatomegaly, and so forth, may have several primary underlying causes just as fever and its associated manifestations may be produced by many factors other than infection. When the syndrome appears in a previously normal animal following administration of DCA, the abnormal physiologic state is DCA intoxication and not heart failure. Only when the clinical syndrome is produced primarily as a result of disease of the heart should it be considered as congestive heart failure. *Therefore, congestive heart failure is, by definition, due to cardiac disease.* Thus, the syndrome cannot be classified as heart failure if the cardiac state is normal in all respects.

It is generally assumed that the syndrome occurs only when the heart fails mechanically as a pump; whereas this concept is probably correct, it has not yet been clearly established. It has not been proved that the syndrome cannot develop as a result of cardiac disease without mechanical failure of the heart as a pump. A theory to support this idea may easily be advanced with but a single plausible assumption. In order to permit continuation of this discussion, however, it will be accepted that in congestive heart failure the heart first fails as a pump.

2. The clinical syndrome of edema, ascites, pleural effusion, basal pulmonary râles, hepatomegaly, dyspnea, and so forth occurs as a result of cardiac dysfunction, probably failure of the pump to eject a sufficient volume of blood. As stated previously, these sequelae, rather than the heart itself, have been under observation by most investigators studying congestive heart failure. Obviously, there is much to learn about these sequelae, particularly changes in the physiologic state responsible for and associated with them.

HEMODYNAMIC CONSIDERATIONS OF CONGESTIVE HEART FAILURE

With the assumption that the clinical syndrome of congestive heart failure is produced by failure of the heart as a pump, we shall next consider the hemodynamic consequences of failure of the pump.

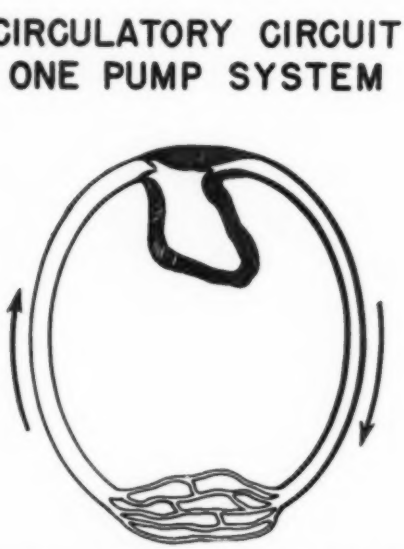

Fig. 3.—Diagram of a circulatory circuit with a single pump. In this and the other diagrams of the circulatory circuit, it is assumed that the subject is resting horizontally. Consult text for details.

The Circulatory Circuit With One Pump.—Consider a pump circulating water around a circular ditch. As long as the pump continues to operate, the water will flow around in the ditch. The energy generated by the pump is lost overcoming the friction due to the flowing water. Should the pump fail, the water would simply stop flowing. It will not dam behind the pump and produce a "congestion" in the portion of the ditch returning water to the pump. The same should be true if the ditch were a closed vascular system with one ventricle generating the energy necessary to force blood around the circuit (Fig. 3). Therefore, failure of a single pump in a vascular circuit should not be expected to produce congestion in the circuit.

The Circulatory Circuit With Two Pumps.—The human vascular system is supplied by two pumps, the right and left ventricles of the heart. This situation poses a different hemodynamic condition from that involving a circulatory circuit supplied by a single pump described in the preceding paragraph. Before various

aspects of the hemodynamic consequences of failure of one or the other pump in the two-pump circulatory circuit are discussed, certain physiologic conditions must be noted.

The *total blood volume* of an average-sized man is about 5,000 c.c., about 500 c.c. of which is in the pulmonary circulatory circuit and about 4,500 c.c. in the systemic circuit. It is important to remember that the potential capacity of the systemic venous system is large, and, therefore, the relative volumes of blood in the systemic and pulmonary venous systems may vary even more widely than indicated by these values. This is especially possible in disease states. The *mean pressures* within the active circulatory system of an average adult resting quietly in the supine position are approximately those recorded in Fig. 4.

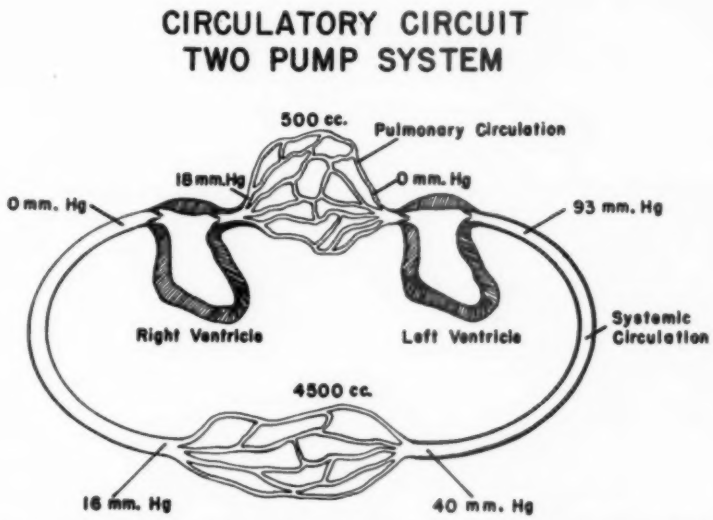

Fig. 4.—Circulatory circuit with a two-pump system, showing average pressures within the circuit. Approximately 500 c.c. of blood are in the pulmonary vessels and 4,500 c.c. in the systemic vessels. In considerations discussed in the text, it is possible to draw an analogy between this two-pump circulatory circuit and a circular ditch with two pumps operating in series near each other and separated only by a small portion of the total length of the ditch.

The heart is a *generator of energy* which is delivered to the blood within the ventricles when they contract upon their contents. The ejected blood conveys the energy beyond the heart into the vessels of the body, the energy existing within the flowing blood as *potential energy and kinetic energy*. The vascular tubes are the conductors of the energy-bearing blood. Potential energy is manifested primarily as lateral pressure, which constitutes most of the blood pressure recorded clinically. Kinetic energy is manifested as energy of flow.

If the circulatory circuit were a frictionless system, once the blood was set into motion, it would continue flowing without cessation and there would be no need for further cardiac contraction or energy from the heart. Such is not the case, however; there is much *friction* within the circulatory circuit. It progressively increases in amount in the arterial system from the heart to the peripheral vessels and decreases in the venous system, progressively declining as the

heart is approached from the peripheral vessels.[28] Because of friction, energy imparted to the blood is lost as heat in the vessels. As the energy is lost, the blood pressure is reduced and differences in pressure in different vessels of the circulatory circuit develop. Thus, as shown by Fig. 4, when the blood is flowing, there is uneven distribution of pressure within the vascular system.

It is obvious that if the heart should stop beating and the lumina of the heart and vessels of the cardiovascular system should remain patent, the pressure throughout the entire vascular system would become equalized, reaching a value of about 85 mm. of water, the *mean systemic pressure* of Weber or mean systemic static pressure (Fig. 5). When the heart stops beating, blood is forced from the vessels of higher pressure to those of lower pressure, i. e., blood will shift from the arterial side of the circulation to the venous side. The easily distended veins accommodate this blood readily without much change in pressure within them.

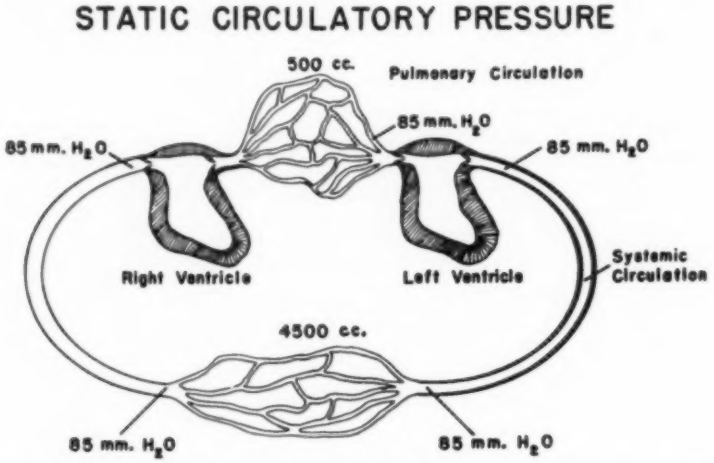

Fig. 5.—The circulatory circuit is shown with the circulation arrested. The system of tubes is patent and continuous. The heart having stopped beating, a static systemic vascular pressure of approximately 85 mm. of water is reached throughout. When the heart stops beating, the distribution of blood is different from that when the circulation is active. Blood is shifted from the arterial side of the circulation, where the pressure is high and the vascular record strong, to the venous portion, where the pressure is lower and the vessels more distensible.

Such was actually found by Starling[9] to be the case for the dog whose heart was made to stop beating temporarily by vagal stimulation. When the vagal tone was released and the heart again pulsated, the blood began to flow, friction produced its influences, and unequal pressures within the vascular system again developed. The differences in pressure began to develop at the first beat. Starr and Rawson[4] obtained similar data in man at death and in his constructed model of the vascular system. Curiously enough, Starling found the pressure in the portal vein of the dog to remain essentially the same whether or not the blood was flowing.

The skeletal and smooth muscles, gravity, and elastic tissues of the body are among other factors which contribute energy to the blood within the vascular system. Except for gravity, these factors make their greatest contribution to the pliable venous portion of the vascular system.[28]

The Vascular System, Blood Volume, and Blood Pressure.—The blood in the vascular system is incompressible. The walls of the vessels enclose or "fit around" the blood. The pressure of the blood within the vessels is determined by the "tightness" with which the vessels fit around the blood. Thus, the blood pressure in the vascular system is determined by the "tone" of the vessels or the volume of the blood or both. Obviously, there can be no disproportion between the volume of the vascular bed and the blood volume. They are always equal in a closed vascular system, even in the presence of surgical and medical shock. When the blood pressure is higher in a given segment of the vascular system, the vessels fit more tightly around or "squeeze" more tightly upon the blood within.

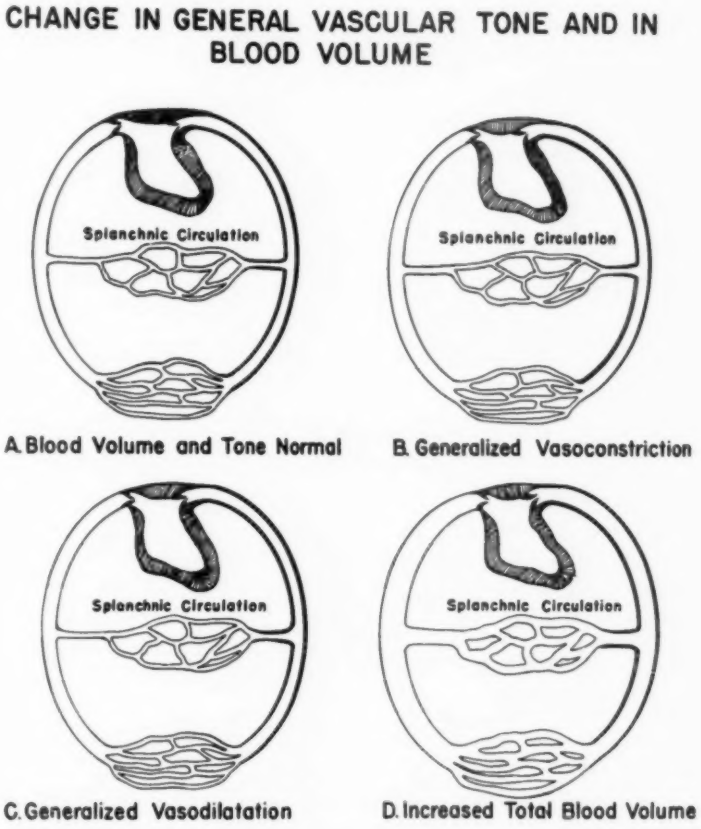

Fig. 6.—Relationship of vascular tone to blood volume. The volume of the vascular bed and blood contained within are always equal. *A*, Normal vascular tone throughout the circulatory system. *B*, Generalized "vasoconstriction" or, more accurately, generalized increase in vascular tone or "tightness of squeeze" of the vascular system on the blood within. This increase in tone does not generally result in a change in volume of the vascular system or blood within or in a change in distribution of blood. There merely results a generalized rise in intravascular pressure. *C*, Generalized vasodilatation or, preferably termed, generalized decrease in vascular tone or decreased "squeeze" of the vascular system on the blood within. Since blood is incompressible and unexpandable, the volume of the vascular system and blood within remain unchanged, but since the squeezing force on the blood is diminished, there is a generalized decline in intravascular pressure. *D*, Increase in blood volume, causing an equal increase in vascular volume. The change in pressure associated with this is determined by the tightness with which the vessels squeeze on the blood within. Should they distend readily, the pressure would rise only slightly, but should they resist distention, the pressure would rise to a higher level.

Conversely, when the walls squeeze less tightly, the pressure declines. During such periods of variations in "tightness of fit" the volume of the blood or vascular bed does not change, since the blood is incompressible and unexpandable (Fig. 6). If the blood volume increases, the volume of the vascular system increases equally. If the vascular walls are "stretched" or pressed upon from within by an increase in blood volume, the blood pressure within must increase, since the walls are resisting distention. If the tone of the entire vascular system were to increase proportionately throughout without a change in blood volume, then the blood pressure throughout would also increase proportionately. The reverse would be true if the vascular tone decreased. With either state of vascular tone, the blood volume and the volume of the vascular bed would, as always, be equal.

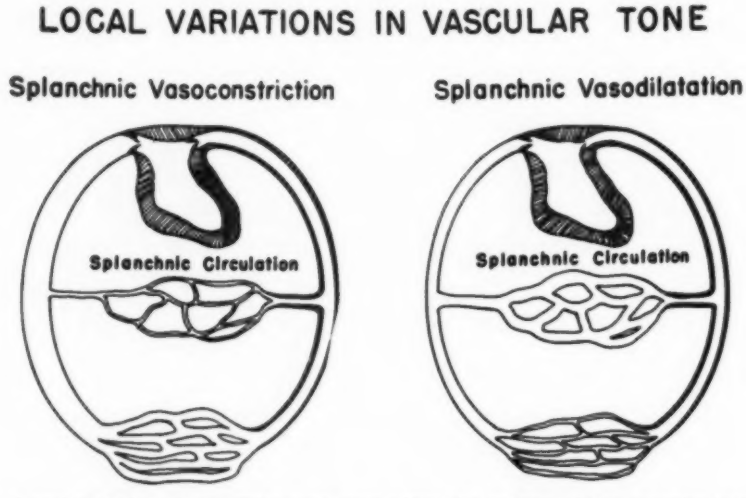

Fig. 7.—Local variations in vascular tone may affect the volume of the vascular bed and blood locally. For example, with splanchnic vasoconstriction, blood is squeezed out of the splanchnic area into other vessels, which must expand an equal volume to accommodate the displaced blood. With splanchnic vasodilatation blood volume and volume of the splanchnic vessels increase equally, but blood must be shifted to them from other vessels, which narrow by an equal volume. During local vasoconstriction or vasodilatation, the volume of blood remains equal to the vascular system generally as well as locally, and the total volume of blood and vascular system need not change.

If there were no change in blood volume under either condition, there would be no vasoconstriction or vasodilatation, i. e., the vessels would not decrease or increase in volume. They would merely tighten or loosen their "squeeze" on the blood within. It is for this reason that the terms "generalized vasoconstriction" and "generalized vasodilatation" may be misnomers or, at least, may lead to errors in thought.

It is obvious, however, that there may actually be localized constriction or dilatation within the vascular system (Fig. 7), i. e., there may be a local reduction or enlargement in the volume of the vascular system. When this occurs, the total blood volume and total volume of the vascular bed need not and probably do not change, and, of course, both always remain equal. For example, if the vessels of the splanchnic area undergo vasoconstriction and decrease in volume by 200 c.c., then exactly 200 c.c. of blood are squeezed out of these vessels.

The blood is shifted into other portions of the vascular system, which must dilate or increase in volume by exactly this same amount to accommodate the shifted blood (Fig. 7). Conversely, if the vessels of the splanchnic area dilate and increase 200 c.c. in volume, then exactly 200 c.c. more blood must flow into these vessels. This additional amount must come from other portions of the vascular system, which must therefore decrease in volume by 200 c.c. (Fig. 7). The concept of hemometakinesia was introduced to define this constant shifting or lending and borrowing of blood among different portions of the vascular system.[29,30]

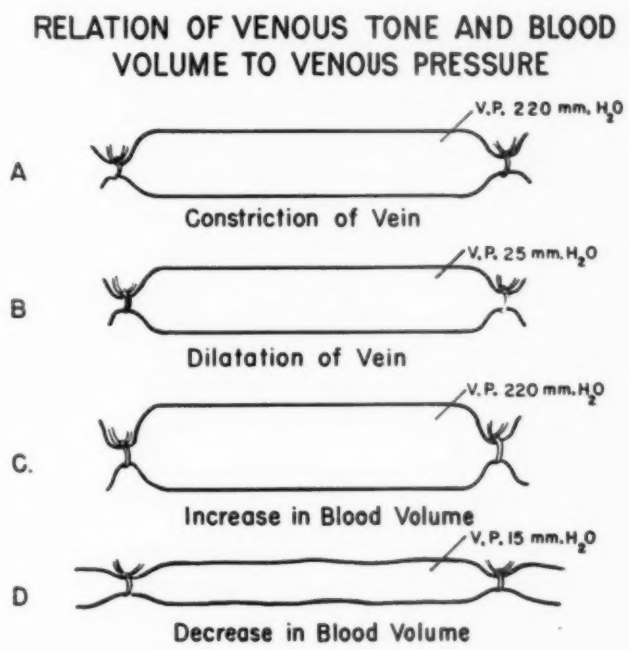

Fig. 8.—Segments of veins showing relationship of venous *tone* and blood volume to venous pressure. *A* and *B* show no change in volume of the segment but considerable change in the pressure within. In *A* there is "venoconstriction" or tightening of the vascular wall on the blood within, causing an increase in venous tone. *B* shows "venodilatation," with less squeezing on the contained blood and consequent decrease in venous tone. It is obvious that the terms constriction and dilatation are misleading in that there is no decrease or increase in the volume of the venous segment, since blood is incompressible and unexpandable. The term "tone" is probably a better one to employ when there is no change in volume. *C* and *D* show changes in venous pressure within the venous segment produced by an increase or decrease in blood volume within the segment and secondarily by the "stretch" placed upon the venous wall.

Thus, whenever the pressure increases in any given segment of the vascular system, for example, the veins, either one or both of the following phenomena must have occurred: (1) the vascular tone or tightness with which the walls of the vessels squeeze upon the blood within must have increased or (2) the volume of blood within must have increased and thus stretched the walls of the vessels (Fig. 8). This must be remembered whenever a change in venous pressure in congestive heart failure is under consideration.

Starling showed many years ago that when the circulation ceases for 20 to 40 seconds, the resulting cerebral ischemia causes the mean systemic pressure

to rise two- to threefold. This "generalized" vasoconstriction includes the venous system. This increase in venous tone may occur in varying amounts, possibly to unequal degrees in different areas of the venous system when there is general circulatory failure, as occurs with impairment of cardiac action. This phenomenon will be discussed again later.

Blood Volume.—It is generally accepted by clinicians that the blood volume remains constant in normal man. This is not absolutely true, however, since all known physiologic phenomena are variable, each with a mean state. The studies of chloride,[22,23,31] water,[32] and sodium[24] turnover in the plasma reveal extremely large quantities of exchange and at rapid rates. The volume of the blood may, therefore, conceivably fluctuate rapidly and in fairly large amounts if mechanisms develop which cause an unequal shift of fluid into or out of the blood vessels. This possibility must be considered when problems related to electrolyte balance and blood volume are encountered.

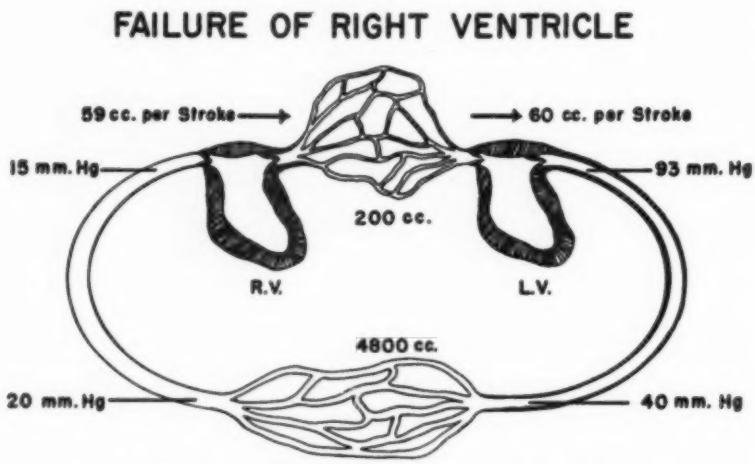

Fig. 9.—Failure of the right ventricle. Consult text for details.

Failure of the Right Ventricle.—A theoretic consideration of the circulatory circuit of the two-pump heart system with failure of the right ventricle as a "pump" is presented in Fig. 4. For example, if the subject is horizontal and at rest with the circulation normal, the blood volume and pressures will be distributed in general as previously discussed. Now if it is assumed that the left ventricle is ejecting 60 c.c. per stroke, then, since equilibrium is present, the right ventricle must also be ejecting 60 c.c. per stroke. Suppose it is now assumed that the right ventricle "fails" slightly and ejects 1 c.c. less, or 59 c.c. per stroke; the left ventricle, not having failed, continues to eject 60 c.c. per stroke (Fig. 9). As a result, with each heartbeat 1 c.c. more of blood will be removed from the pulmonary circuit by the left ventricle than is delivered to it by the right ventricle. And if the cardiac rate is 100 beats per minute, then every minute 100 c.c. of blood will be shifted from the pulmonary vessels to the systemic ones. In five minutes all 500 c.c. of blood within the pulmonary vessels then would theoretically be removed from the pulmonary system. This obviously could not occur. After

a time (five minutes in this case), the left ventricle could eject no more blood per stroke than the right ventricle delivered to it and then the output of the left ventricle per stroke would be determined by that of the right ventricle. In this case the volume of the left ventricular stroke would decline to 59 c.c.

Now if it is assumed that all the blood from the pulmonary system were shifted to the systemic system by means of "failure" of the right ventricle, a disturbance in systemic circulation would not be expected as a result of the shift alone. This should produce no greater disturbance in the systemic circulation than a transfusion of 500 c.c. of blood. In both instances, because of the low pressure and great distensibility of the venous system, the blood finds its way into the veins or venous reservoir. The veins distend, and if their "tone" or "tightness of squeeze" remains constant, the venous volume will increase without an associated significant rise in venous pressure. Such a response of veins to a relatively small increase in blood within them is normal.[35] After some time, blood would reaccumulate in the pulmonary vessels, and a new steady state would be reached with both ventricles ejecting 59 c.c. per beat because, actually, there are slight differences in output between the two ventricles from moment to moment.

If the discrepancy between stroke volume of the right and left ventricles were greater and the cardiac rate were still 100, then the pulmonary vessels would empty more rapidly. For example, if the right ventricle failed and ejected 55 c.c. per beat while the left ventricle ejected 60 c.c., the pulmonary vessels would theoretically be expected to be emptied in one minute. Thus, the crucial changes may take place too rapidly to be readily observed.

It is evident, therefore, that merely failure of the right ventricle to pump sufficiently cannot cause an elevation in venous pressure because of damming of blood behind the right ventricle. Only a slight or no rise in venous pressure would be expected to occur if there were simply a dam in the stream. If, on the other hand, failure of the heart as a pump were the initiating cause for the clinical syndrome of congestive heart failure, then other factors would have to participate. The mechanism and time of their appearance remain unknown.

Incidentally, it is apparent from the foregoing discussion that if the venae cavae entering the right atrium were suddenly occluded by means of a hemostat (Fig. 10), there should be no more significant damming of blood behind the heart than Starling found when he suddenly made the dog's heart stop beating by vagal stimulation. When the venae cavae become completely occluded, the stroke output of the right ventricle would suddenly decline to zero. The left ventricle would empty the pulmonary vessels of blood within a few beats and then the output of the left ventricle would become zero. The arterial blood pressure would fall and blood would be shifted to the systemic veins from the pulmonary vessels and systemic arterial system, and the static systemic pressure would be obtained. The resilient and distensible veins would accommodate the blood shifted to them from the vessels of higher pressure with little change in venous pressure. A rise in venous pressure to high levels could only be brought about by an increase in the tightness with which the veins squeezed upon the blood within. Without this increase in venous tone, no significant rise in venous pressure would be expected. Exercise of skeletal muscle or pressure upon the

liver will increase the pressure in the veins in direct proportion to the tightness or tone of the venous system. Merely a dam in the stream located in or near the right atrium would therefore not be expected to produce severe venous hypertension or congestion of blood under pressure.

On the other hand, in obstruction to the pulmonary veins or in pure mitral stenosis, the hemodynamic disturbances produced in the pulmonary vessels would differ considerably from those described with clamping of the superior and inferior venae cavae. For example, with obstruction of the pulmonary veins blood pumped by the right ventricle would tend to accumulate behind the

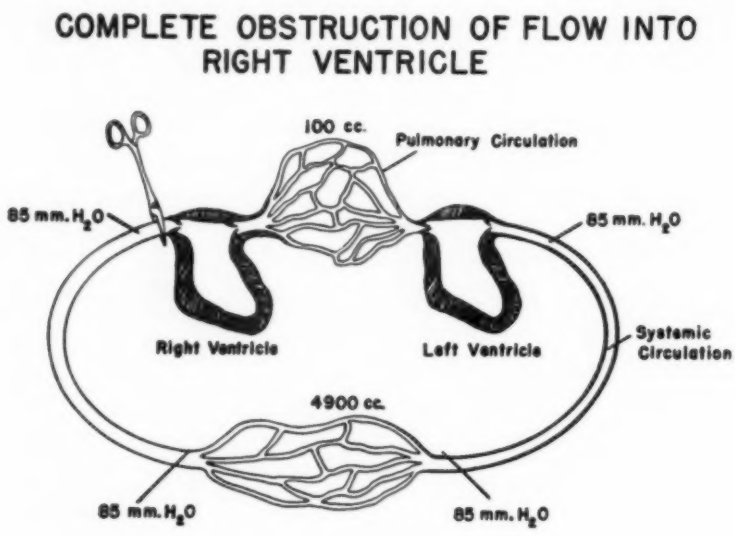

Fig. 10.—Complete obstruction of the return flow to the right ventricle produced by a clamp. This causes the intravascular pressure to reach the static systemic level. Consult text for details.

obstruction. Since the systemic blood volume is relatively large and the potential volume of the pulmonary vascular system relatively small, the additional blood forced into the latter will increase either the vascular tone or stretching of the vessels or both and thus cause the pressure in the pulmonary veins as well as arteries to rise. This would increase hydrostatic pressure in the pulmonary vessels and produce the well-known clinical manifestations of pulmonary intravascular hypertension. Pulmonary edema would develop readily, since intracapillary pressure is also elevated. The clinical picture of pulmonary edema or "congestive heart failure" would develop. The acuteness and severity of this picture would depend upon the rapidity and degree of development of the obstruction.

The hemodynamic pattern for mitral stenosis is similar to that described for obstruction to the pulmonary veins. The details of pressure and volume flow are obvious and are predictable. Although no clinical syndrome produced by spasm of the pulmonary vein has been described, should such a clinical counterpart occur from local venous spasm or as a result of external pressure, the associated hemodynamic phenomena would be predictable.

That the syndrome develops in cardiac disease in association with an excess of intake over output of electrolytes and water is well known. It is possible that when the output of the ventricles drops below a certain *critical level*, the other mechanisms producing the syndrome of congestive heart failure are set into motion by yet unknown processes. These may be humoral (hormonal included), acting generally and specifically upon the kidney to cause a decrease in urinary output. They may also be partially hemodynamic in nature, influencing glomerular filtration and renal blood flow. These factors are discussed later in greater detail.

When the critical level of failure of the pumping mechanism is reached the venous pressure may rise because of an increase in blood volume, due to retention of electrolytes and water, or because of an increase in venous tone (possibly due to cerebral asphyxia or release of neurogenic or chemical venopressor substances). Surely either increased blood volume or increased venous tone alone or both can account for the elevation of the venous pressure. However, it is unlikely that the changes in blood volume alone encountered in congestive heart failure are of sufficient magnitude to account for the change in venous pressure.

The fundamental mechanisms by which the complete clinical syndrome finally develops remain unknown and the detailed nature of the trigger mechanism and the chain of events leading to the syndrome are yet to be established. Only limited aspects of these are known. The initiating mechanism of congestive heart failure may be related to the relative amount of decline in cardiac output, to circulatory demands of the tissues, or to cardiac insufficiency. The following concept is often advanced. Cardiac reserve cannot be measured quantitatively, not even as quantitatively as renal function. It is roughly estimated by means of the functional classification employed clinically.[34] It may be assumed that normal cardiac function is 100 per cent, i. e., it is able to meet the needs of the body under ordinary demands of human activity. As with any other organ of the body, cardiac function can probably be reduced to some degree without significantly interfering with circulation to the tissues. However, with continued decline in function cardiac output becomes insufficient to supply certain demands placed upon it. With mild failure, it may not be able to cope with the demands of strenuous exercise but may satisfy lesser needs. With more extensive failure, the heart cannot even meet the demands placed upon it during ordinary living or even during bed rest. When the demands exceed the cardiac functional capacity for a sufficient time, the mechanisms concerned with producing the syndrome of congestive heart failure are brought into operation and the resulting chain of events which lead to the clinical syndrome are set into motion.

It is important to remember that under most clinical circumstances congestive heart failure begins slowly, presenting diurnal variations. During the day when the demands placed upon the heart are greatest, the demands of the tissues cannot be satisfied so that edema and other associated manifestations develop. During the night when the individual is in bed, the demands of the tissues decline to a level below the maximum functional capacity of the heart and compensation

sets in. This day-and-night cycle of relative failure and relative compensation may continue for weeks. If each day, for example, the physiologic phenomena of failure exceed the amount of compensation achieved during the night, the sum total phenomena of failure accumulated over a period of several days or weeks will be great enough to be manifested clinically. The nature of the cycle and rate of change may vary considerably, depending upon the activity, diet, presence of infections, therapy, severity of the cardiac disease, and many other factors obtained by the subject.

In the case of "high output" failure, even though the output is relatively high by comparison with the usual instances of heart failure, it is still insufficient to meet the current tissue needs, so that certain mechanisms are initiated and the syndrome of congestive failure develops. It must be remembered that these concepts are purely speculative, being based primarily upon indirect evidence and reasoning.

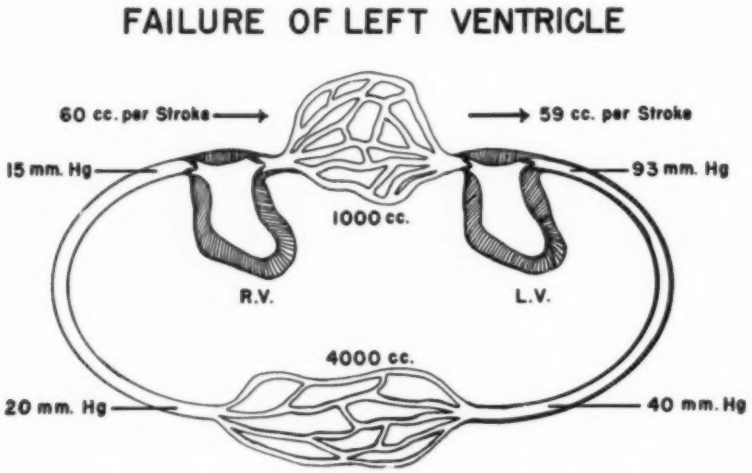

Fig. 11.—Failure of left ventricle. Consult text for details.

Failure of the Left Ventricle.—When the left ventricle fails in the two-pump circulatory circuit, the hemodynamic outcome is different from that described for failure of the right ventricle. For example, when each of the two ventricles ejects 60 c.c. per stroke, the circulation is maintained in a normal state. If the left ventricle fails slightly and ejects only 59 c.c. per stroke, then 1 c.c. more blood will be pumped by the right ventricle than by the left (Fig. 11). This results in an accumulation in the pulmonary vessels of 100 c.c. of blood per minute if the cardiac rate is 100. In five minutes 500 c.c. would be shifted from the systemic circulation into the pulmonary system. Because of the relatively large volume of the systemic circulation, a sufficient quantity of blood may be shifted into the pulmonary vessels to produce congestion and the clinical picture of acute pulmonary edema or "left ventricular congestive heart failure." Therefore, the syndrome of pure left ventricular failure is possible upon congestion or a dam in the stream alone. The greater the discrepancies between the outputs of the left and right ventricles, the more rapidly will congestion develop.

After a time the right ventricle will eject no more blood than the left ventricle removes from the pulmonary vessels per stroke, and a new state of equilibrium will be re-established with each ventricle again ejecting an equal volume. The systemic venous pressure would not change significantly because of the capacity of the veins to accommodate their volume to the volume of blood within them. The venous return to the right ventricle should not decline and interfere with the right ventricular stroke volume unless a large volume of blood were trapped by an extremely distensible pulmonary vascular system. If the left ventricular output is reduced to a level too low to meet the needs of the tissues, the mechanisms responsible for the syndrome of congestive heart failure (anasarca, hepatomegaly, ascites, pleural effusion, venous hypertension, and so forth) would be initiated, these mechanisms being similar to those for failure of the right ventricle.

Failure of Both Ventricles Simultaneously.—If it is assumed that the syndrome of congestive heart failure is produced by equal and simultaneous failure of both ventricles, the changes in the hemodynamic state would be similar to those described for failure of the single pump of the circulatory circuit in a one-pump system. There obviously could be no damming of blood in the stream, for reasons discussed previously. There would be no more accumulation of fluid behind any one ventricle than if two pumps situated fairly closely together in a circular ditch simultaneously failed equally to some degree but continued to pump equal volumes of water around the ditch. The water would remain equally distributed throughout the ditch and no damming of water would occur.

Should both ventricles fail simultaneously but unequally, then the hemodynamic changes expected would depend upon which ventricle failed to the greater degree. The results of both of these situations have been described. It is evident that failure of both ventricles simultaneously does not significantly modify the hemodynamic principles previously described for failure of the "pump."

ROLE OF THE KIDNEYS

From the foregoing discussion, it is evident that, except for acute left ventricular failure, the entire clinical syndrome of chronic congestive heart failure cannot develop from disturbances in hemodynamics alone. Other physiologic processes are necessary for the development of the syndrome.

There are certain physiologic processes which function during the development of the syndrome:

1. The syndrome, by definition, begins with disturbances in the heart.

2. The water and electrolytes which are retained enter through the gastrointestinal tract, and there is no evidence that the intake is abnormally large.

3. Renal excretion of water and electrolytes must be less than intake, for a positive balance must exist in order for anasarca to develop in the patient. Since the intake is essentially unchanged, renal function must change and the urinary output must be decreased.

Clinicians have known for many years that a renal factor exists in congestive heart failure. Patients with progressive congestive heart failure are known to

have scanty, highly colored urine of high specific gravity containing albumin, casts, and erythrocytes. Intake of electrolytes and water is known to produce exacerbations of the syndrome. That renal function is only temporarily disturbed or altered is evidenced by the rapid return of previous renal function with the onset of compensation and diuresis. Furthermore, administration of a mercurial diuretic to a patient in congestive heart failure with reduced urinary output, including sodium and water, promptly produces diuresis. Such a response is not obtained in a patient with terminal nephritis. Thus it is evident that the kidneys are not diseased in uncomplicated congestive heart failure, and although they may function differently, this is not necessarily abnormal for such a cardiac state. Furthermore, an intake of sodium below the level of output results in clinical improvement.

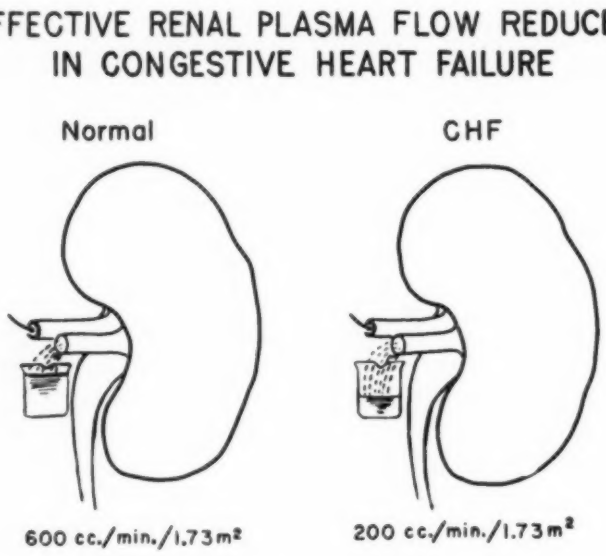

Fig. 12.—Effective renal plasma flow changed from an average normal of 600 c.c. to 200 c.c. per minute per 1.73 m^2.

Renal Function.—Studies of renal function[35-42] have shown that it is altered during cardiac decompensation. As with cardiac output, the findings have varied with the degree and stage of the failure. Not only is the state of the failure important, but so are its duration, acuteness of onset, and chronicity.[40] Because of such factors, general psychic and physical state of the subject under study, and errors in clearance methods, results of observations concerning renal function in congestive heart failure have varied considerably.[36-39,41,42] These variations in results have naturally led to differences in conclusions and to some confusion concerning the renal physiology associated with failure. Therefore, with the data available it is not possible to define precisely the renal function or changes in renal function associated with the syndrome of chronic congestive heart failure. The physiologic renal state which is most generally accepted by those engaged in such studies is presented. It is well to realize that the variations may be considerable.

In general, effective *renal plasma flow* (RPF) has been found to decline from a mean normal value of about 600 to as low as 200 c.c. per minute per 1.73 m^2 (Fig. 12). *Glomerular filtration rate* (GFR) has been observed to decline from a normal mean value of about 100 c.c. to 75 c.c. per minute per 1.73 m^2 (Fig. 13).

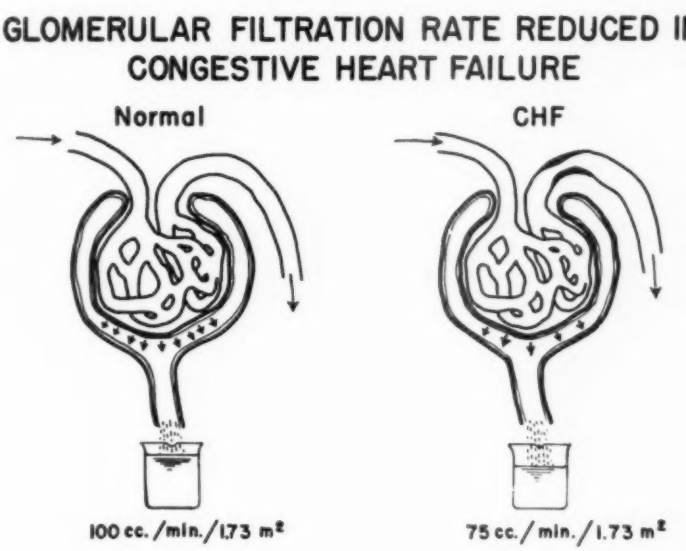

Fig. 13.—Glomerular filtration rate reduced in congestive heart failure from an average normal of 100 c.c. to 75 c.c. per minute per 1.73 m^2.

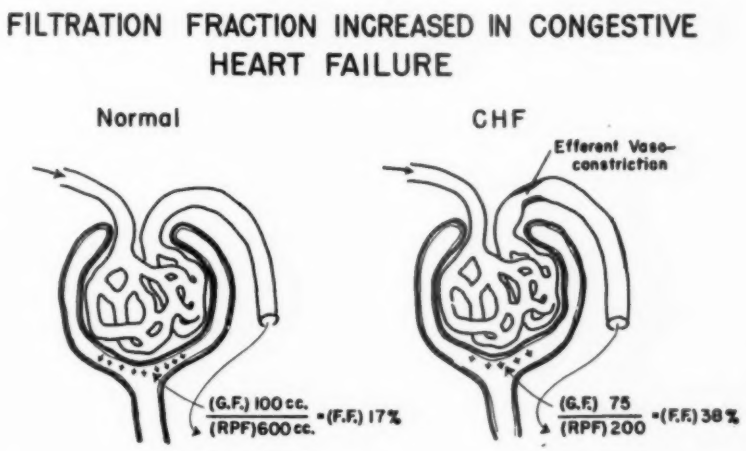

Fig. 14.—Filtration fraction may be increased more than twofold in congestive heart failure. This apparently occurs because of constriction of the efferent glomerular arterioles.

The *filtration fraction* (FF), on the other hand, has been seen to rise from a normal value of about 17 per cent to about 40 per cent (Fig. 14). The *maximum tubular capacity of excretion of para-aminohippurate* (T_{mPAH}) may decline from a normal mean value of 80 to 44 mg. per minute per 1.73 m^2. These clearance studies indi-

cate a reduction of about 65 per cent in effective renal plasma flow in congestive heart failure. The rate of glomerular filtration is reduced about 25 per cent, but the filtration fraction may be more than doubled. In order for the filtration fraction to increase and still conform to generally accepted concepts of formation of urine, efferent arteriolar constriction must develop. This results in greater extraction from the blood flowing through the glomeruli. The significance of the decline in maximum tubular capacity is not clear.

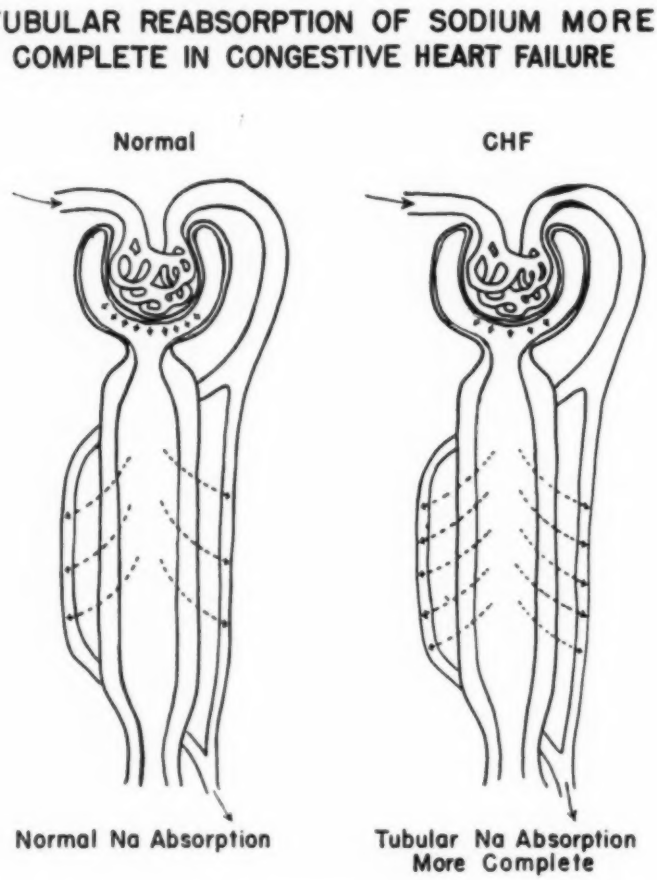

Fig. 15.—The tubules reabsorb sodium more completely in congestive heart failure. The mechanism and precise location of this reaction remain unknown.

There is no general agreement about how and why renal function is changed in congestive heart failure. Many investigators are interested in this at present. Almost everyone agrees that there is more complete tubular reabsorption of sodium from the glomerular filtrate as it passes through the nephrons (Fig. 15). Although the mechanism by which this occurs remains obscure, some observers[43,44] have interpreted their data to indicate that the increased tubular reabsorption is localized in the distal tubules. The experiments do not unequivocally establish

this concept, the conclusion being based upon crucial assumptions which have not been definitely proved. Furthermore, studies in this field have not demonstrated that changes in the hemodynamic state alone are sufficient to explain all the changes in renal function observed in congestive heart failure. Considerable data[3,45,46,47] indicate that humoral or chemical factors mediated through the tubules are at least partially responsible for changes in renal function.

None of the renal studies indicate primary renal disease; only altered function has been observed. Whether or not this change in function is compensatory or obligatory remains unknown at present, but it is probably both.

ROLE OF THE ENDOCRINE SYSTEM

Because of the relatively rapid rate with which the changes in renal function occur and because of the nature of these changes, it has been suggested by those interested in the problem that excretion of sodium and water is reduced because of excessive production or failure of inactivation of water- and electrolyte-retaining hormones.[3,42,45,48,49] To date evidence for this is indirect and speculative, based upon the close similarity of the urinary changes observed in congestive heart failure to those associated with administration of adrenocorticotropic hormone, desoxycorticosterone acetate, and other steroids. Obviously, the suprarenal and pituitary glands have been considered the sites of the hormone production. These concepts may eventually prove to be true, but today they remain speculative. It is not always that which appears to be most logical that finally proves to be the true mechanism.

It is possible to propose a chemical chain of events to explain the mechanism for electrolyte and water retention mediated through the kidneys in which the primarily responsible chemical agent acts as an inhibitor or an activator, but the mechanism for the activation of such an agent is unknown. This chemical chain of events is probably extremely complex, as are most of the known metabolic processes. The pituitary and adrenal glands may be and probably are concerned with them, but this is not necessarily true.

Antidiuretic substances have been detected in the urine of patients with congestive heart failure.[46] The presence of such a substance might be expected in the urine of any patient with nonmechanical or functional oliguria, but its significance has not been established.

It may be concluded from speculation and evidence that a chemical mediator or chain of chemical processes is associated with retention of electrolytes and water as a possible cause of the reduced excretory function of the kidneys in congestive heart failure. Much more extensive research is yet required to clarify the problem, however. It is not proposed to review here in detail the evidence for and against a chemical factor in congestive heart failure or to indicate the research requirements and discrepancies.

VENOUS HYPERTENSION

That generalized and symmetric venous hypertension is associated with congestive heart failure is generally accepted. The precise time relationship to

each and all of the physiologic disturbances observed in the various stages of congestive heart failure remains obscure. Some observers contend that venous hypertension precedes the accumulation of fluid and electrolytes; others believe it follows or coincides with the accumulation. The experimental data in support of either concept are insufficient to permit definite conclusions. Regardless of this, however, some theoretic considerations appear applicable.

For example, it has been pointed out that venous hypertension cannot occur without either or both: (1) an increase in venous tone or "tightness of squeeze" of the venous walls upon the blood within or (2) an increase in blood volume within the veins. If it is shown that venous pressure increases during the early stages of congestive heart failure or when the "pump" or ventricle fails and before the patient accumulates water and salt, then either there is an increase in venous tone or the blood volume is increased at the expense of interstitial or intracellular water and electrolytes, or both of these occur. If, on the other hand, it is shown that the patient gains weight or accumulates water and salt before or simultaneously with a rise in venous pressure, then an increase in blood volume may be a factor, but an increase in venous tone most likely also contributes to the venous hypertension, for the magnitude of increase in blood volume reported is not sufficient in itself to cause venous hypertension. Should there be no change in blood volume during the period of rise in venous pressure, then an increase in venous tone must be the direct cause of the venous hypertension, for it has been shown in the foregoing discussion that a shift of blood from the pulmonary circuit cannot cause an elevation in systemic venous pressure with failure of the pump alone.

It is also important to remember that distended veins in the neck do not necessarily indicate an increase in blood volume. As stated previously (Fig. 7), blood may be shifted from one portion of the circulation to another without a change in blood volume. The distended veins may, therefore, indicate a more intense localized venous tone or a constriction of the more peripheral veins or, at least, of veins elsewhere.

It is interesting to note that there are no satisfactory data to establish the presence or absence of an increase in venous tone during the developmental phases of the syndrome of congestive heart failure. The studies of McMichael and his associates do not and, as designed, could not settle this point. The state of venous tone is obviously an important problem which has received little, if any, direct examination.

It is known that pressure over the liver (hepatojugular reflux) or exercise results in an increase in venous pressure in patients with congestive heart failure, whereas it produces little or no rise in normal subjects. The mechanism for the elevation in venous pressure has likewise never been elucidated. If either the blood volume or the venous tone is increased, pressure over the liver, which displaces blood out of the liver or splanchnic vessels, or muscular activity with associated displacement of blood out of the veins within the skeletal muscles into the large systemic veins would be expected to cause a definite elevation in venous pressure. In the normal subject, displacement of the blood into normal veins with normal tonal function and a normal content of blood would not be expected

to produce a significant elevation in venous pressure. Normal veins under normal conditions accommodate a relatively large volume of blood without an increase in intravenous pressure.[3] It is also possible that the venous tonal regulating mechanisms may be more sensitive to shifts in blood or changes in venous hemodynamics in the subject with congestive failure than in the normal person.

Experimental injury to the right ventricle to produce "failure" of that ventricle results in a physiologic state in which exercise of skeletal muscles causes a rise in venous pressure.[21] Such experiments are difficult to interpret because of the numerous variables involved and the complexity of the state of the experimental animal, including change in blood pressure, cardiac rate, and possibly vascular tonal function. Before it can be concluded that venous hypertension is the result of a dam in the stream, the state of venous tone or reactivity of venous tone to a shift of blood into the systemic venous system must be evaluated. If venous tone were increased directly by contraction of the smooth muscles within the walls of the veins or increased by a shift of blood into the large systemic veins associated with a greater response to passive distention, then venous pressure would rise in association with exercise. Surely the level of venous pressure or a change in that level is not a reliable index of the accumulation or "damming" of blood behind a failing ventricle. That the level of venous pressure tends to bear a relationship to the clinical state of congestive heart failure is well known. A spontaneous rise or fall in venous pressure does not a priori, however, indicate the existence of or a change in a "dam in the circulatory stream" or suggest that congestive heart failure consists merely of passive congestion of blood in the veins.

CLINICAL SUGGESTIONS

Although concepts concerning the mechanism of congestive heart failure have been revised during the past few years, these changes have not been sufficiently significant to warrant a modification of the clinical management. The use of morphine, oxygen, digitalis, low-salt diet, and mercurial diuretics dates back twenty or more years in some clinics. It is, therefore, important for the clinician to govern therapy by previous clinical experience. Changes in management are indicated only when proved necessary.

Today we know that the mechanism of congestive heart failure is considerably more complex than previously considered by most clinicians and physiologists. The two classical concepts of backward and forward failure are obviously not sufficient in themselves to explain the syndrome of failure. Nevertheless, clinical experience based upon interpretation of these two concepts has been responsible for certain generally accepted approaches to the management of patients with congestive heart failure. Until the problem is more clearly elucidated, these methods of clinical management and consideration should be continued and modified only as progress dictates.

From the clinical point of view, it has been learned that "left ventricular congestive heart failure" may be associated with certain manifestations, for example, cardiac type of dyspnea, accentuated P_2, protodiastolic gallop rhythm, basal râles, pulsus alternans, and roentgenographic signs. "Right ventricular congestive heart failure" is usually accompanied by generalized and symmetric

venous hypertension, hepatomegaly, dependent edema, ascites, and pleural effusion. Management of these syndromes depends upon the detailed clinical manifestations, complications, underlying cardiac disease, and clinical course, to mention only a few factors. Therapeutic measures must continue to be employed, of course, while the mechanism of congestive heart failure is being further studied. Furthermore, from the clinical point of view the terminology employed is irrelevant, and whether it is or is not possible for one ventricle to fail separately is likewise immaterial. The management of patients is most successful by certain approaches.

A comparison may be made with diabetes mellitus. Its clinical management remains unchanged regardless of whether or not the concept of beta-oxidation of the fatty acids is correct. All therapy is not being discontinued until that point is completely clarified. Similarly, the clinical management of congestive failure will have to continue to be empiric to some degree. Terms with erroneous implications may continue to be employed for traditional reasons. This is permissible, provided the clinician is thoroughly aware of the lack of knowledge concerning the mechanism of failure. He should be prepared to change his concepts whenever new data become adequately established. To change the terminology prematurely and without adequate supporting evidence, however, can only lead to further confusion.

SUMMARY

The numerous aspects of the mechanism of congestive heart failure herein presented attest to the extremely complex nature of the clinical syndrome. Many phenomena are concerned with production of the various manifestations of the syndrome. It appears certain that although an increase in venous pressure contributes to the formation of edema, it is not the only factor responsible, nor does the venous hypertension result solely from a "dam in the stream." Chronic congestive heart failure cannot be explained simply on the basis of the mechanisms previously defined by the backward or forward concepts. There are many important, interesting, and incompletely understood hemodynamic phenomena associated with heart failure. The role of the kidneys, of the endocrine system, and of cellular or enzymatic phenomena are presently being investigated. These factors are probably important contributors to the syndrome of congestive heart failure; their precise role is unknown. The foregoing discussion does not constitute a review of the literature but rather a brief, and surely incomplete, presentation of the problem. Certain hemodynamic principles have been emphasized which seem to escape the consideration of most clinicians and, at times, even of those especially interested in the syndrome.

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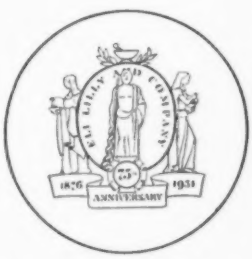

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